MARCH, 1953

The Review of Gastroenterology

OFFICIAL PUBLICATION

NATIONAL GASTROENTEROLOGICAL ASSOCIATION

The General Adaptation Syndrome (G-A-S) and Gastroenterology

Some Recent Progress in Gastrointestinal Physiology

Several Problems in Benign Biliary Tract Surgery

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Eighteenth Annual Convention

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VOLUME 20 NUMBER 3

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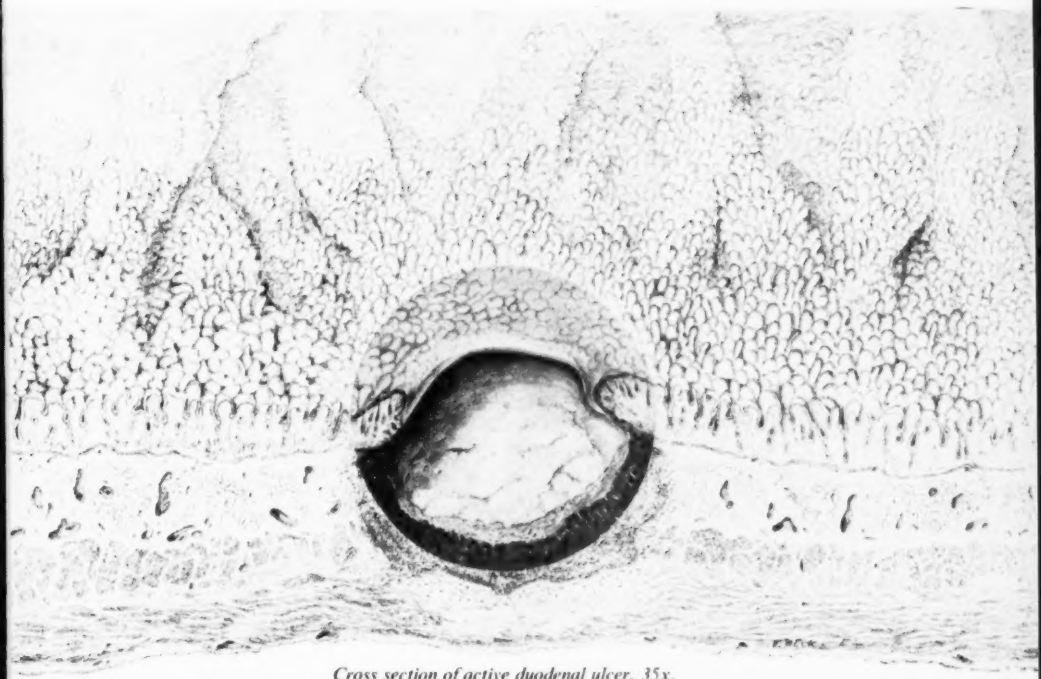

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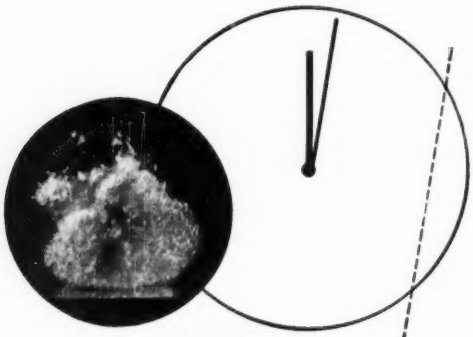

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(INCORPORATING THE AMERICAN JOURNAL OF GASTROENTEROLOGY)

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VOLUME 20 MARCH, 1953 NUMBER 3

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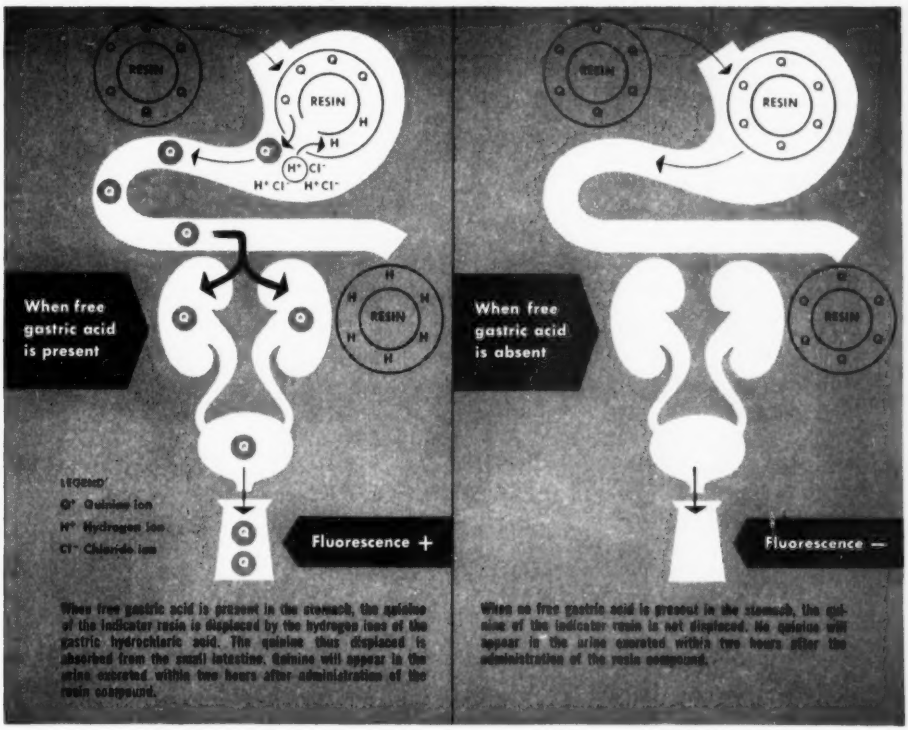

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The Review of Gastroenterology

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Volume 20 MARCH, 1953 Number 3

SEVERAL PROBLEMS IN BENIGN BILIARY TRACT SURGERY*†

HERBERT F. NEWMAN, M.D.

New York, N. Y.

Surgery for benign biliary tract disease has afforded symptomatic cure in only 60 to 80 per cent of the cases. Study of our failures has revealed that the responsibility resides in one or more factors:

First, a poor choice of candidate for surgery.

Second, insufficient knowledge of the pathologic anatomy and physiology in the entire duct system of the case explored.

Third, a poor selection of surgical procedure.

Fourth, a poorly executed operation.

Our first problem concerns the choice of a patient in whom surgery may be expected to effect a cure. Most clinics have reported a higher percentage of symptomatic improvement following surgery in cases with calculi than in the noncalculous disorders. In some institutions, preoperative proof of cholelithiasis is a prerequisite for elective surgery. This attitude will elevate the percentage of good results following surgery, but will not increase the total number of patients that may benefit by it.

I should like to present three types of noncalculous functional biliary disease wherein surgery may be expected to give relief.

Case 1:—The first is exemplified by a 28 year old nulligravida with a five year history of repeated severe biliary colic which usually followed meals. Cholecystography revealed a normal gallbladder with excellent concentration of dye. Within four minutes after a fat meal, she developed severe right upper quadrant pain and nausea. A film taken at that moment showed that the gallbladder had evacuated about three-quarters of its contents within this short interval (Fig 1).

*Read before the Seventeenth Annual Convention of the National Gastroenterological Association, New York, N. Y., 20, 21, 22 October 1952.

†This investigation was supported by a research grant from the National Institute of Health, Public Health Service.

At operation, an anatomically normal gallbladder was removed. On follow-up, there has been no recurrence of pain and the patient can tolerate large doses of fat without symptoms. It is suggested that in this case the humoral response to fat evoked a massive, painful contraction of the gallbladder. The precise nature of this phenomenon is obscure but we may use the analogy of hyperthyroidism, the etiology of which is equally unknown, but in which clinical relief is gained by resection of the end-organ.

Case 2:—The second case is a 42 year old male with a similar history of biliary colic usually precipitated by meals. Here too, a fat meal induced a typical

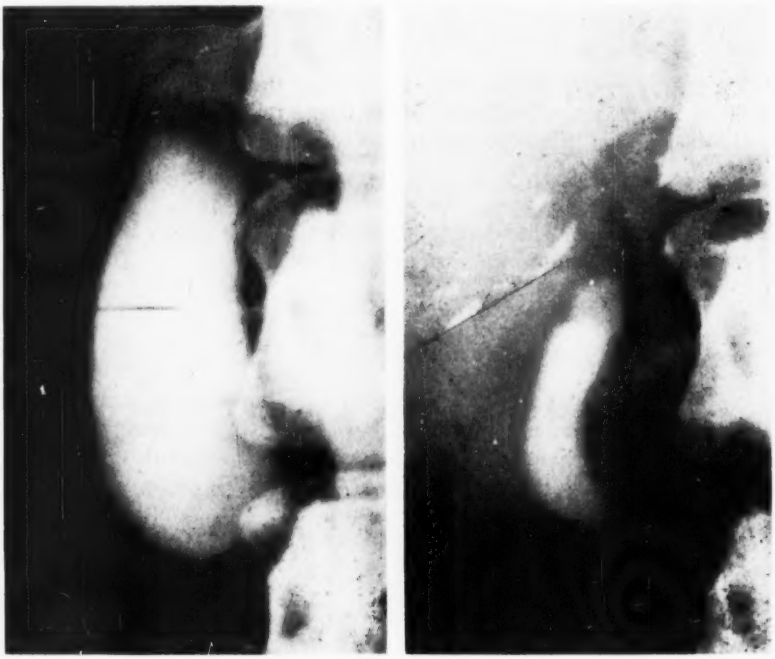

Fig. 1

colic but, in contrast to the first case, there was roentgen evidence that the gallbladder failed to empty at all within two hours. At operation, the gallbladder was grossly normal, but the valve-free segment of the cystic duct adjacent to the common duct had so narrow a lumen that it failed to admit the finest lachrymal probe. Cholecystectomy effected a complete relief of symptoms. In this case, contraction of the gallbladder against an anatomically narrow cystic duct evoked pain.

Case 3:—The third case is that of a 54 year old multigravida with a three year history of frequent attacks of right upper quadrant pain radiating to the

back and epigastrium. Cholecystography revealed a slightly larger than normal gallbladder with normal response to fat meal. In the course of a rather sustained attack, her serum bilirubin and alkaline phosphatase rose to double the upper limits of normal. At exploration, the gallbladder was grossly normal. The common duct was two centimeters in diameter. The papilla of Vater protruded into the duodenal lumen as an easily palpable button-like structure. Only the finest probe could be passed through the sphincter which was rigid in consistency. External sphincterotomy was performed. This case is unique in my experience and has been operated upon too recently to evaluate the end-result. These three types had in common a history of biliary colic, some confirmatory evidence, preoperatively, of biliary tract dysfunction and anatomically normal gallbladders at operation.

The problem of noncalculous chronic cholecystitis is more complex. In a review of 3,458 cases of acute cholecystitis, stones were not found in 10.6 per

Fig 2

cent. This suggests the relative incidence of chronic cholecystitis without stones. The direct etiology of the acute processes in these cases is often obscure and it is hoped that cholangiography may unravel the primary mechanism. From a limited experience with these cases, it is our impression that the basic obstruction is usually lower in the biliary tract, explaining the low incidence of symptomatic relief after cholecystectomy alone. Adequate surgery may help the severe cases but the major problem is one of diagnosis and choice of the appropriate procedure.

Our second major problem embraces a thorough awareness of all the aberrant physiology and anatomy in the case chosen for surgery. Although much information may be secured preoperatively, an enormous amount of supplemental knowledge can only be obtained at the table. Vision and palpation may be satisfactory modes of evaluation of the gallbladder, but both are inadequate for the ducts or sphincters. Here we are primarily concerned with four possible lesions: stones,

benign stenoses, tumor, and functional sustained contractions called "spasms". Often there are multiple lesions. Concretions are frequently found aobve regions of stenosis. Classifying direct cholangiography as a form of exploration, it is my belief that, wherever feasible, the duct system should always be explored. Stones may be present in the common duct without any vidence of dilatation of the duct or a history pointing to their presence.

Is acute cholecystitis a deterrent to exploration of the common duct? In a collected review of 25,807 cholecystectomies done largely for chronic biliary tract disease, common duct stones were found in 11.3 per cent compared to 9.0 per cent of 3,484 cases of acute cholecystitis[2]. Follow-up of many cases of cholecystectomy for acute cholecystitis demonstrates common duct stones overlooked at the primary procedure. If the patient with acute cholecystitis is jaundiced, there is a 52 per cent chance of finding a common duct stone which is about the same chance in a case of chronic cholelithiasis with jaundice. Furthermore, there are a definite number of acute cholecystidites wherein obstruction is not found at the gallbladder neck or cystic duct but lower in the duct system. In the last year, I have encountered two cases of carcinoma of the head of the pancreas whose first manifestations were those of acute cholecystitis without obstructing stones. There is little evidence that the introduction of water soluble iodine compounds into the common duct in the presence of acute cholecystitis produces any damage.

Methods of exploration of the ducts are multiple. Direct exploration through an incision in the cystic or common ducts with probes, scoops, sounds, catheters or dilators leaves much to be desired. Soft intraductular or ampullary tumors may not be recognized. A calculus may occupy a pseudodiverticulum in the preampullary region and be passed by a Bakes dilator. Calculi or stenoses in the hepatic radicles cannot be reached. In the tortuous type of common ducts seen after long-standing pancreatitis or common duct disease, such exploration is actually hazardous with the risk of forming a false passage (Fig. 2). Only in the most advanced cases, can the exact status of the sphincter of Oddi be evaluated with a probe. My personal experience with the lithophone has not been satisfactory for the characteristic click is not secured with soft stones. The use of ultrasonic scanning devices is restricted to the detection of calculi.

Table cholangiography is an excellent method of exploration and its virtues have been thoroughly expounded in the literature. In the presence of acute cholecystitis, injection of the dye through the stump of the cystic duct is a safe technic in those cases where the structures of gastrohepatic omentum are so infiltrated that direct injection of the common duct is technically difficult. Our major difficulty with operative cholangiograms has been in the interpretation of the sphincter zone. The presence of dye in the duodenum merely bespeaks some degree of patency of the sphincter but may not tell us "how patent" and whether the opening into the duodenum is of a rigid or elastic nature. Frequently the film is taken during a phase of active contraction of the sphincter and the

terminal portion of the duct is not visualized at all. It is specifically in this group of cases that operative manometric determinations may complement our information.

The French have employed table manometric studies of the biliary system for at least ten years and Mallet-Guy's book is a beautiful compilation of hundreds of carefully studied cases. His technic involved the injection into the biliary tree of enough saline to produce what he calls "hyperpressure", recorded by a tambour on a motor-driven drum. His interpretation is then deduced from both the height and character of the pressure tracing secured during the period immediately following cessation of fluid injection. Static pressure can occur in the biliary system only in the presence of both complete cessation of hepatic secre-

Fig. 3

tion and total distal obstruction. In referring to pressure in the biliary system, we are usually referring to "perfusion" pressure or the side pressure in a system with two major variables: the rate of inflow of fluid and the cross-sectional area of the sphincteric orifice. The ducts are relatively nondistensible and variations in the size of ducts in different patients are reflected primarily in the speed rather than the height at which perfusion levels are reached.

The method I have used for biliary system manometry is simpler than Mallet-Guy's and less subject to criticism on a physiological basis. A flowmeter, mounted below the level of the patient, is connected by rubber tubing to a flask of saline held at least four feet above this level. From the flowmeter, by means of a Y tube, saline flows through a cannula inserted into the duct; the other arm of

the Y ends in a glass manometer. By means of a tunnel clamp, the rate of flow of saline can be regulated between 0 and 50 c.c. per minute. Saline is dripped into the system at the rate of 0.5 c.c. per minute until a stable level of pressure is reached. The rate of flow is slowly increased while pressure is recorded until the pressure rises to some predetermined level, as 300 mm. of saline. Such minor fluctuations in pressure as appear spontaneously or secondary to respiration are ignored.

The pressure reached at a perfusion rate of 0.5 c.c. per minute represents the pressure during a normal rate of hepatic secretion. Mallet-Guy reports 180 mm. of saline as the upper level of normal pressure, but does not state his perfusion rate. Most of our normals level off at a much lower level, at our 0.5 c.c. per minute rate. In a patient with a normal sphincter of Oddi, increasing the rate of flow does not substantially increase the pressure in the system until extremely rapid rates of flow are induced. No doubt this is due to progressive dilatation of the sphincteric orifice which adjusts to maintain a stable level of pressure as flow increases. Exactly the same phenomenon is seen on insufflating the uterus and tubes in performing a Rubin test but in both cases it is essential that the increments of flow be added slowly. In ten presumably normal common ducts, the pressure levels did not rise on speeding the flow up to 10 c.c. per minute and, in one case, the pressure remained at 60 mm. of saline up to a rate of 70 c.c. per minute. We are in the process of translating these findings into a number which would represent the actual cross-sectional area of the sphincteric orifice. At the rate of 20 c.c. per minute, a pressure head of 180 mm. of saline is secured with an opening as small as the lumen of the hub of a No. 18 hypodermic needle. Further investigation into what comprises a normal sphincter is urgently needed.

The reproduction of a cholangiogram in Figure 3 demonstrates the frequent difficulty in interpretation of the status of the sphincter. Table manometrics in this case revealed a stable level of pressure of 80 mm. saline at a flow rate up to 12 c.c. of saline per minute. This was considered normal and the patient's postoperative course and delayed cholangiograms confirmed this impression, illustrating the complementary value of manometrics to cholangiography.

Partial obstructions are seen in cases of tumor infiltration, early benign stenosis, Odditis or hypertrophy of the sphincter, common duct stones, and invariably in the postoperative course of those patients whose sphincters had been traumatized by exploring instruments. Hydrodynamically, it is manifested by step response to increasing the rate of flow, the normal degree of accommodation being absent. It can be mimicked by small doses of morphine in a normal patient, i.e.

Rate of flow	*Pressure level*
1.0 c.c./min.	220 mm.
3.0 c.c./min.	240 mm.
4.0 c.c./min.	280 mm.
7.0 c.c./min.	320 mm.

In a case of jaundice due to partial obstruction by a stone in the ampulla, the pressure levels were:

Rate of flow	*Pressure level*
1.0 c.c./min.	150 mm.
2.0 c.c./min.	180 mm.
4.0 c.c./min.	270 mm.

After the calculus was removed, the level remained at 150 mm. of saline with a rate of flow up to 7.0 c.c. per minute. It is interesting that the pressure secured while the stone was *in situ* and partially obstructing the duct was within the normal range at a low rate of perfusion flow and its obstructing in-

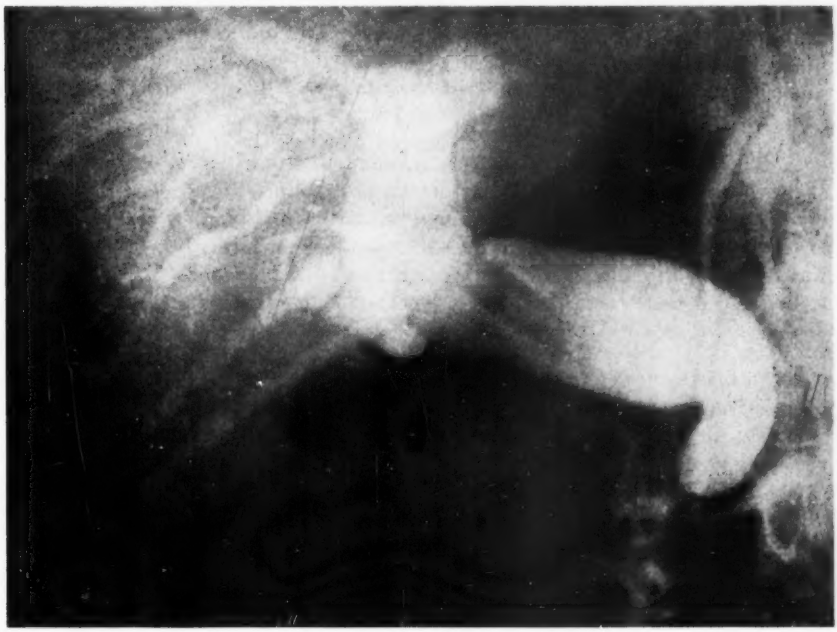

Fig. 4

fluence became manifest only at the more rapid rates of perfusion. This may explain Hicken and McAllister's finding of normal intraductal pressures in cases of obstructive jaundice due to stone. In their cases the pressure in the common duct was secured by a needle attached to a manometer and presumably at a flow rate produced only by the patient's own hepatic secretion. In several observations, I have found the rate of hepatic secretion in the human under anesthesia to be less than 0.5 c.c. per minute.

In total obstructions due to carcinoma or some impacted calculi, the pressure rises indefinitely at very low rates of perfusion and no level is secured. In one

case, x-ray revealed two calculi in the gallbladder but at operation, neither was found in the excised organ and the patient had no evidence of common duct obstruction. Manometric study at the table showed total obstruction. Both stones were found jammed in the ampulla where they produced total obstruction for such a short period that neither jaundice nor dilatation of the ducts was produced.

The cholangiogram in Figure 4 is that of an 88 year old male who had a cholecystectomy for acute cholecystitis and a secondary choledochostomy for an overlooked stone in the common duct. At this latter operation, the terminal portion of the common duct was explored with sounds and scoops. Manometry performed one week later and repeated at weekly intervals for three months has shown a persistent level of 450 mm. of saline at a perfusion of 0.5 c.c. per minute. Amyl nitrate inhalation produced either no effect or the gasping incident to its inhalation produced an actual rise in pressure. We suspect that we have induced organic stenosis of the sphincter, as has been reported by Adams from the Lahey Clinic.

Manometric determinations finds tremendous value in testing the efficacy of procedures employed for treating benign obstruction. Wide open choledochoduodenostomies or other shunts of course permit tremendous rates of flow without any significant effect on common duct pressure. In one case, where the sphincter was dilated with the largest Bakes dilator, this same phenomenon was found at the table but, when repeated several weeks later, the sphincter had contracted down to evoke a normal response to change of flow.

Our final problem concerns the choice of procedure to be employed in benign obstructive disease of the sphincter. The syndrome of "spasm" probably occurs and may merit surgery, but at present we demand direct evidence of partial obstruction proved by manometrics. In these cases, the orifice of the papilla is either tightly stenosed or the papilla itself is so grossly enlarged as to be easily palpable through the duodenum. In these latter cases, we are not in a position to tell whether the lesion is a true hypertrophy of the musculature or the result of inflammation. We do not know the upper limits of mass of a normal sphincter muscle and biopsies have revealed very meager signs of inflammation.

Five procedures merit consideration: 1. Endodochal dilatation with a graded series of Bakes dilators is a blind procedure with the ever present danger of creating a false passage. One of my patients had an immediate massive intraduodenal hemorrhage following its usage. We are inclined to agree with Zollinger on the danger of subsequent stenosis. I cannot find any reports of proof by cholangiography or manometry that the sphincter remains dilated for any length of time.

2. Endodochal sphincterotomy is similarly a blind procedure which, in our hands, was more apt to cut only the papillary fibres than the more important circular fibres embracing the common duct proximal to the papilla.

3. Extraduodenal sphincterotomy has been performed six times on our service and will be the subject of a later report by Dr. Lee Gillette.

4. Choledochoduodenostomy or enterostomy gives excellent functional results but has the disadvantage of a stormy postoperative course and prolonged maintenance of a T tube *in situ*.

5. Transduodenal sphincterotomy has the advantage of visualization of the papilla so that early neoplasms are not overlooked and a large wedge of muscle may be excised. At present it seems the method of choice.

Summary

1. Three types of functional biliary tract diseases which may respond to surgery are presented.

2. Common duct exploration of some type is recommended in all cases with cholangiography the method of choice in acute cholecystitis.

3. The value of table manometry as a complement to cholangiography is discussed.

4. The choice of operative procedure for benign sphincter obstruction is outlined.

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Discussion

Dr. Samuel Gaines (New York, N. Y.):—Dr. Newman has given us a presentation of problems encountered in gallbladder surgery. He has discussed noncalculous gallbladder disease, the problem of diagnosing obscure common duct stones, and also disturbances of the sphincter of Oddi.

I should like to first discuss acute calculous cholecystitis with or without stones in the common duct, and chronic cholecystitis without stones. There has been considerable discussion recently about the time of operation for acute cholecystitis, first as an emergency operation, just like an acute appendicitis; second, intermediate operation, giving the patient time for adequate hydration and working up the patient with blood counts, and so forth; and, third, medical treatment, and then operation at the interval period.

With our accumulated experience it has been shown that there is great danger in giving antibiotics to these patients, as a false sense of security is obtained, and the gallbladder may rupture with very, very few warning symptoms. I remember one case which I saw on Saturday night, a case scheduled for operation on Monday morning. When the patient was operated upon Monday morning the gallbladder had ruptured, with very few symptoms.

Now we come to the problem of what operation is to be performed in acute cholecystitis. In over 95 per cent of them, cholecystectomy will be the operation of choice; however, cholecystostomy still has a place; given a very sick, elderly patient with a gallbladder in a very difficult position, a cholecystostomy will be life-saving.

Should one explore the common duct in acute cholecystitis? We are dealing with edematous tissues, and with tissues that are very friable. In my experience the great majority of cases of acute cholecystitis are usually accompanied by a stone in the cystic duct, and once the gallbladder is removed, a cholecystectomy will give a perfect functional result. In the occasional case in which you suspect a common duct stone, palpation will usually reveal a suspicious area, and then an exploration of the common duct can be done.

In chronic cholecystitis the story is entirely different. Opening the common duct is a relatively safe procedure, but it does lead to increased morbidity and mortality. In an average case a simple cholecystectomy requires about one week of hospitalization. Once we open the common duct, not only is morbidity increased but also the mortality. Cholecystectomy nowadays should not have a mortality of more than one-half of a per cent; however, choledochostomy will increase the mortality to perhaps three or four times that per cent, and, of course, the hospitalization, instead of being one week, is delayed perhaps anywhere from three to six weeks.

Now, Glenn, for instance, has reported a mortality in choledochotomy of 4 per cent. Occasionally some surgeons will report smaller mortalities for small

numbers of cases. For this reason, common duct exploration should not be a routine procedure but each case should be carefully studied for indications. Thus, the incidence of common duct stone increases with the duration of the disease. The longer the patient has gallstones, the greater the chance that some stones will find their way into the common duct.

I make a suggestion at this time that there is no such thing as a symptomless gallstone. If you question the patient, symptoms of indigestion, flatulence and bloating will be elicited.

The presence of common duct stones should be suspected when there is a history of jaundice or intermittent elevation of temperature. While jaundice in itself is not an absolute sign of common duct obstruction, it should act as a red flag or rather a yellow flag and extra caution should be used. Other indications for exploration are a dilated cystic duct, enlarged head of pancreas and palpable stones in the common duct.

With these criteria as a basis, I believe that only in about 10 to 15 per cent of cholecystectomies will exploration of the common duct be required. Thus Glenn, at the New York Hospital, in a series of over 3,000 cholecystectomies, had exploration performed in about 10 per cent, and stones removed in 65 per cent of the 10 per cent, leaving a corrected percentage of about 7 per cent of the total.

In those cases where the common duct is open, it should be explored thoroughly either by palpation or by cholangiogram, or by the manometric pressure readings, or the method suggested by Dr. Newman. In a rather unscientific way, we have been using his method whereby we put a tube in the common duct, and see whether fluid will flow readily by gravity into the common duct; however, this is subject to error because it merely gives us a picture of the distal portion of the common duct. It does not give us a picture of the proximal portion.

In the same way cholangiograms are also subject to error. I have seen postoperative cholangiograms showing shadows suggestive of stones, and then at operation no stones could be found.

But all these methods are worthy of trial in the difficult cases where stones are suspected in the common duct, or other lesions in the common duct or in the sphincter of Oddi.

Now let us take up noncalculous cholecystitis. Dr. Newman has mentioned a figure of 60 per cent. In gallbladder disease, if we exclude noncalculous gallbladder, we will approach a figure of 95 per cent of cures, or over, which is an extremely good result in the treatment of any disease, and, in my opinion, noncalculous gallbladder disturbances are essentially medical. Surgeons have assumed the treatment of so many diseases that I feel it is about time that we left something for the gastroenterologists to do. These patients should receive medical care for prolonged periods and occasionally have cholecystograms done as a check; with a thorough, prolonged study, I am convinced that very few of these

patients will reach the operating room. In the rare case that we do operate and find no stones, as a rule we leave the gallbladder alone.

As a result of this conservation, the proportion of noncalculous gallbladders removed at operation is gradually diminishing.

Now, as to disturbances of the sphincter of Oddi, these belong with the so-called dyskinesias of the gallbladder. In all cases where gallstones have been removed, I believe that disturbances of the sphincter are due to inflammatory reactions either around the sphincter itself or in the pancreas.

I might cite a personal case. This was a doctor's mother, who had a long history of gallbladder disease. She was brought into the hospital with an extremely acute gallbladder. She was too sick to have a cholecystectomy, so a cholecystostomy was done, with the removal of stones. Following operation, a cholangiogram was done, and was perfectly normal. When the opening closed, a few weeks later, the patient developed severe abdominal pain. I reoperated upon her, suspecting a residual stone in the common duct. I removed the gallbladder at that time, put a probe in the common duct, and no stones were found, and I did a cholangiogram at that time, and also no suspicious shadows were found. After a few weeks she again developed the same type of pain and she went to another surgeon who operated upon her for suspected common duct stones. He found no stones, but he found a thickening of the sphincter of Oddi, and this time he did a sphincterotomy, and after two months the patient had exactly the same symptoms. She was reoperated upon, and a transduodenal sphincterotomy was performed, and this time she stayed cured.

I believe that these patients, therefore, where there is a real disturbance of the sphincter of Oddi, should have a thorough exploration through the duodenum and a thorough sphincterotomy performed.

COMPLETE SITUS VISCERUS INVERSUS ASSOCIATED WITH CHOLELITHIASIS AND COMPLICATED BY CARCINOMA OF THE GALLBLADDER*

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This study was undertaken after a review of the literature failed to reveal any recent authenticated case similar to this one.

Stall[1] of Vienna, in 1777, published the first authentic record of two cases in which autopsy was performed. One of these was spectacular, the patient having

Fig. 1

transposition of the viscera, with carcinoma in a gallbladder situated on the left side. No mention, however, was made to the effect that it was a complete situs

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viscerus inversus, and it must be presumed the transposition was confined entirely to the abdominal viscera.

Situs inversus, less commonly called transposition of viscera or heterotaxia, has been known from ancient times. Aristotle[2] cited two cases of transposed organs in animals. Fabricus[3], in 1600 A.D., described a case of transposed liver and spleen in a human being. Fehsemeyer[4], in 1897, demonstrated the condition by roentgen rays.

In reviewing the literature from 1926 to 1946 inclusive, Johnson[5] found 632 cases of situs inversus of which there were 515 examples of dextrocardia, 379

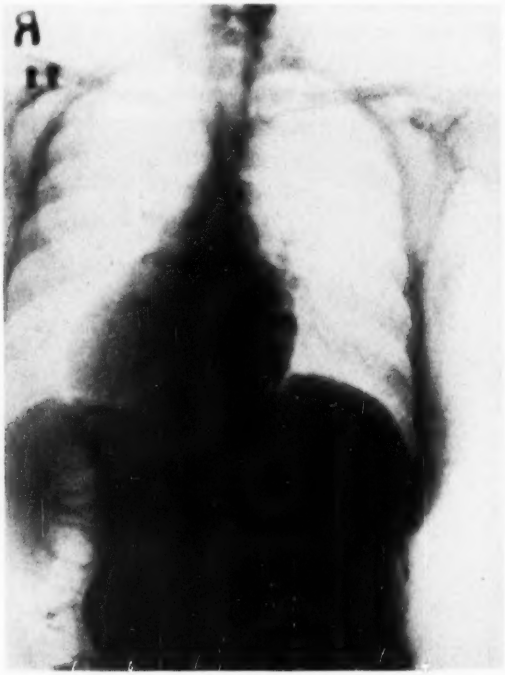

Fig. 2

instances of situs inversus totalis, 128 persons in whom dextrocardia was known to be the only form of transposition, 41 cases of partial situs inversus, 46 cases involving only the colon, 20 cases involving only the great vessels of the heart, 6 cases involving the stomach alone and 2 cases involving the liver alone.

During the years of 1910 through 1947, of 1,551,047 patients registered at the Mayo Clinic, 76 were found on physical and roentgenologic examination or both, to have situs inversus of both thoracic and abdominal viscera. Seven others showed thoracic transposition only and four more had transposition of the viscera

that was confined to the abdomen according to Mayo[6]. This gives an incidence of 0.00489 per cent for complete situs inversus or 1 in 20,408 registrations. In the same period the condition was noted three times in 19,287 necropies.

Adams and Churchill[7], in 1937, found an incidence of complete situs inversus of 0.002 per cent in the patients admitted to the Massachusetts General Hospital and an incidence of 1 in more than 8,000 necropies.

Mayo also found that only two of the 76 patients had any family history of situs inversus. Two men state that they each had a brother (not a twin) with the

Fig. 3

same condition. Torgersen[8] found only six instances of the condition in 573 Siblings of patients with complete situs inversus. He also states there was six instances in which transposition occurred in three Siblings and 19 instances in which the condition occurred in two Siblings. Only one instance has been reported in which both mother and daughter were so affected.

Mayo[6] found seven of the 75 patients had biliary disease. Two of the seven were infants who had congenital atresia or obliteration of the bile ducts associated with complete situs inversus.

Rossien[9], in 1942, reported a case of complete heterotaxia with obstructive jaundice in an elderly female, but the true condition was never determined.

Fish[10], reporting on 11,614 autopsies performed at the University of Michigan Hospital, states there has been a total of 27 cases of primary malignancy of the gallbladder, an incidence of 0.23 per cent.

It has been estimated that in 1936 some 6,500 persons died of this disease in the United States alone, yet in spite of the growing awareness of this type of neoplasm the chance for cure is little better today than it was 175 years ago, when it was first recognized.

Carcinoma of the gallbladder comprises about 6 per cent of all malignant neoplasms. Ewing[11] has stated that the disease occurs four to five times as frequently in females as in males. It appeared more often in the older age group varying from a 13 year old treated by Biering[12] in 1946 to a 95 year old female reported by Kaufman[13]. Fish found the average age for his group of 27 patients to be 56.8 years.

Courvoisier[14] as early as 1890 called attention to the almost constant association of gallstones with carcinoma of the gallbladder. Most reports give an incidence of 73 per cent to 90 per cent.

The incidence of malignant neoplasms of the gallbladder is far higher in patients suffering from cholelithiasis than in the general population. Finsterer[15] stated that carcinoma of the gallbladder developed in five of 114 patients with cholelithiasis who were treated without operation for 10 to 25 years.

While gallstones cannot be proved to cause malignant neoplasia of the gallbladder, there is as Cole[16] has said, "Such a definite relationship between carcinoma of the gallbladder and cholelithiasis, that there can be no doubt about the presence of stones being a factor in the production of the tumor."

Histologically, malignancy of the gallbladder may be divided into two groups. Those derived from the epithelium and the others from the supporting tissue. The epithelial tumors are by far the most frequent and the adenocarcinoma comprise about 85 per cent, the others being equally divided between the squamous cell and mixed types. Papillomata of the gallbladder are rarely associated with carcinoma of the gallbladder.

Neoplasia of the gallbladder spreads to the liver very early and by several methods. The most frequent is by direct extension to the contiguous liver tissue and by infiltration through the lymphatics connecting the subserosal plexus of the gallbladder with the lymphatic channels of the adjacent surface of the liver. Both of these modes of spread produce a single secondary tumor continuous with the primary one, and fairly well limited to the liver substance about the gallbladder fossa. Next in frequency and usually occurring at a later stage, is metastasis through the lymphatics. Accompanying the cystic duct to the signal

node of Lund, at the junction of the cystic and common bile duct and thence through the channels accompanying the common hepatic duct and portal vein to the hilus of the liver. A hematogenous spread to the quadrate lobe may occur rather late.

Clinical considerations of malignancy of the gallbladder present no distinct picture or pathognomonic signs. Signs and symptoms are weight loss, pain, jaundice, abdominal tenderness, hepatomegaly, nausea, vomiting, pruritus and abdominal tumor.

Fig. 4

This unusual case report was a female, Mrs. L. D., age 60, whose chief complaint was pain in left upper abdomen. She stated that for the past eight months she had had pain in the left upper abdomen, which radiated into her back and up into the shoulder blades. It has been more or less continuous with loss of appetite, weakness and weight loss, from 155 to 118 pounds; food intolerance to meat, onions, greasy foods. She stated that she had attacks of pain while carrying her children, whose ages are 33 and 20 years at the present time. Also she had an attack of jaundice when she was pregnant with her second child 20 years ago, which lasted for a period of three weeks.

Review of Systems:—Was essentially normal.

Physical Examination:—Patient is an elderly adult female who seems to have lost weight. Eyes: react to light and in accommodation. Ears and Nose: negative. Teeth: upper and lower plates. Tonsils: small. Neck: no adenitis. Thyroid: palpable. Breasts: no masses or tenderness. Lungs: no rales. Resonant throughout. Heart Sounds: The apex beat is heard and palpated in the right 5th anterior interspace. Heart sounds are rather faint. BP 140/80. Abdomen: Marked tender-

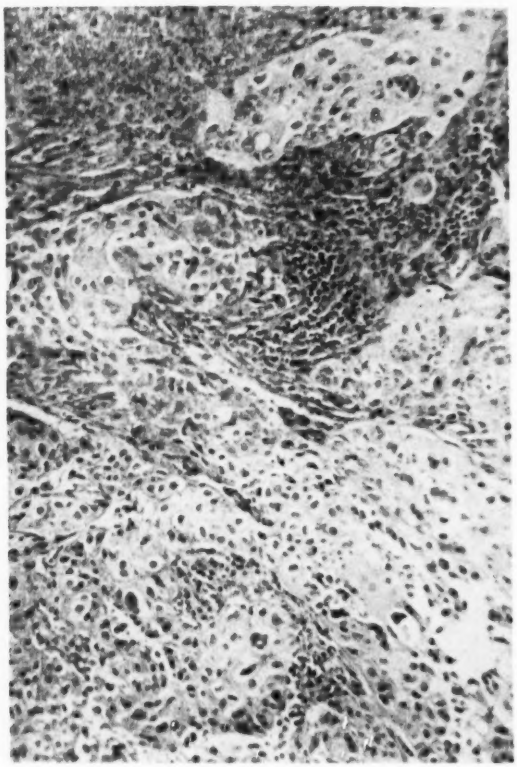

Fig. 5

ness high up in the left upper quadrant of the abdomen, with a palpable mass. Right seems normal, as well as the lower abdomen. Pelvic Examination: Introitus admits two fingers. Bladder and rectum in good position. Cervix: small. Uterus: small and atrophic. Adnexa: negative. Rectal Examination: negative. Lower Extremities: negative.

X-ray of the chest reveals a dextrocardia and the gallstones could be visualized in the left upper quadrant.

Diagnosis:–Complete situs viscerus inversus with cholelithiasis and possibly malignancy of the gallbladder was made March 1, 1950.

Surgical exploration was done through a left upper transverse skin incision, which revealed complete abdominal situs viscerus inversus. Chronic cholecystitis, cholelithiasis and malignancy of the gallbladder was proved by biopsy on opening the gallbladder. There was also metastasis into the liver substance. The wound was closed. Two months following surgery she developed a diarrhea. X-rays were taken July 3, 1950 revealing a fistula between the midportion of the duodenum and colon.

Summary

A review of the literature of situs viscerus inversus and carcinoma of the gallbladder is presented.

A case history of carcinoma of the gallbladder in a patient with complete situs viscerus inversus is given in detail.

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SOME RECENT PROGRESS IN GASTROINTESTINAL PHYSIOLOGY*

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In preparing a discussion of recent advances one has to decide whether to attempt a superficial survey of a large field or to make a more careful analysis of a few outstanding achievements. I have chosen the latter alternative as being both more to my liking and, probably, more profitable for my audience. It happens that during the last few years the significant contributions to gastrointestinal physiology have had to do with problems involved in the nervous and hormonal regulation of gastrointestinal functions and more particularly, with the control of gastric secretion. A brief survey of the status of these problems previous to the period covered by this survey may be in order.

The gastrointestinal muscles and glands are known to be regulated through the various divisions of the autonomic nervous system, sympathetic, parasympathetic and enteric. The role of the sympathetic has never been clearly defined and is, apparently dispensable so far as effective regulation is concerned. The parasympathetic and enteric divisions are closely related, the latter being the terminal complex of the former. The enteric, comprising the plexuses of Meissner and Auerbach, has many functional possibilities which are often overlooked. Since the classic demonstration of the myenteric reflex by Bayliss and Starling it has been known that the enteric plexuses are capable of reflex activity, not dependent on the extrinsic innervation.

The functional relationship between the vagi and the enteric plexuses is not certainly known but the most probable concept is that proposed by A. J. Carlson[1] in 1922. He compared the enteric plexuses to spinal reflex centers and the vagi to the connecting neurones which bring these centers into relation with other centers in the brain. Elaborating somewhat upon this concept we can visualize the vagus impulses as playing upon the synapses of the local enteric reflex arcs, in consequence of which the local reflexes are either facilitated or inhibited. In addition just as voluntary muscular contraction can be initiated by way of the descending spinal tracts, utilizing the efferent limb of the spinal reflex arc as the final common pathway to the muscles, so can the vagi initiate visceral activity through the efferent limb of the enteric reflex arcs. Both the enteric and parasympathetic divisions of the autonomic system are cholinergic; consequently the impulses which they convey release acetylcholine. Some of this will be released by impulses traversing the local reflex arcs and this will be increased by impulses coming over the vagi. The resultant activity will be determined by the total

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amount released. In this way reinforcement of local reflexes through vagus impulses causes the release of a greater amount of acetylcholine at the neuro-effector junction. As a result of this arrangement activities dependent on acetylcholine may be initiated through local reflexes or by way of the vagi or, most effectively, through the combined action of the two.

With regard to the gastrointestinal hormones, we scarcely need review the concepts that have been prevalent until recently. Secretin is well known; pancreozymin has come to be recognized as a companion hormone to secretin, specifically for secretion of pancreatic enzymes[2,3]. Gastrin has been repeatedly extracted from the pyloric mucosa and proved to be chemically unrelated to histamine[4-9], but like histamine, to stimulate chiefly (or exclusively) the parietal cells[4]. Enterocrinin[10] and cholecystokinin[11] are probably functional hormones. A host of other hormones from the duodenal mucosa have been partially identified or suspected, so many in fact that Nasset[12] has referred to the duodenal mucosa as the "hypophysis of the abdomen". An excellent review of the literature in this field has recently been prepared by Grossman[8].

One aspect of the nervous and humoral regulation of function that has recently come under scrutiny has to do with the relationships that exist between the nervous mechanisms on the one hand and the hormonal mechanisms on the other.

The following possibilities may be considered:

1. That the two mechanisms are not related and that each acts independently of the other.

2. That a nervous mechanism is involved in the release of the hormones but their action on the effector cells is independent of the nervous regulation.

3. That the hormones are released through a nervous mechanism and are, in turn, essential for the proper nervous regulation of the effector cells.

Various combinations and variations of the last two possibilities may be considered and also the probability that a particular concept may be applicable to one of the hormones and not necessarily to the others.

When the hormones were first discovered they were generally regarded as independent agents, supplementing perhaps, but in no way dependent on the nervous regulation. This concept was not, so far as I know, ever put into words but it so dominated the thinking of physiologists that the evidence to the contrary which appeared from time to time was not given serious consideration. It was not until Uvnäs[13] in 1942 reported his surprising observations on the relation between the cephalic and gastric phases of gastric secretion that physiologists in general began to consider seriously the possibility that hormonal and nervous regulation of gastric secretion might be closely integrated and that each might be to some extent dependent on the other. Uvnäs' observations indicated that neither the hormonal nor the nervous mechanism could function independently

but that each required the cooperation of the other. We shall discuss this work in detail later on but first we must mention some earlier observations which pointed the way to Uvnäs' startling discoveries.

As early as 1911, Zeljony and Savich[14] had reported that the effect on gastric secretions of applying certain secretagogues to the pyloric mucosa could be prevented by atropine or by applying cocaine to the pyloric mucous membrane. At first the authors thought that their experiments excluded the possibility of a pyloric hormone but Savich[15] later came to the conclusion that a hormone was released from the pyloric mucosa through some nervous mechanism. Straaten[16] in 1933 had observed that little or no free acid was secreted during sham feeding in dogs from which the pyloric portion of the stomach had been removed. He advanced the theory that the pyloric part of the stomach is essential for the development of the cephalic phase of gastric secretion. In 1941 Gregory and Ivy[17] confirmed and extended the observations of Zeljony and Savich. Using dogs with transplanted fundic pouches, they observed that although the fundic pouch normally secreted when the remainder of the stomach including the pyloric antrum, was stimulated, either chemically or mechanically, no such effect was obtained if the mucosa of the stimulated part was first treated with cocaine or procaine. These observations established the fact that the mechanism that was blocked by cocaine includes a hormone, in all probability, gastrin.

In some of these studies and in the work of Uvnäs[13] two different aspects of the gastric secretory problem are involved, the mechanism of the release of gastrin from the pyloric part of the stomach and the possible role of gastrin in the cephalic phase of gastric secretion.

Release of Gastrin Through Local Reflexes

The fact that atropine as well as cocaine interferes with the release of gastrin from the pyloric mucosa suggests that a cholinergic neural mechanism is involved in the process. Recent work leaves little doubt that such is the case. For example, Robertson, Grossman and their co-workers[18] found that application of acetylcholine to isolated pyloric pouches caused secretion in isolated fundic pouches. Adequate control experiments eliminated the possibility that the acetylcholine was absorbed in sufficient amount to affect the fundic pouches directly. Their conclusions are worth quoting. They believe that there is "a nervous arrangement in which the nervous receptors on the mucosal surface are responsive to chemical or mechanical stimulation. These receptors can be inactivated . . . by cocaine. Activation of these receptors leads to a cholinergic discharge at the neuroeffector junction of the cell forming gastrin (probably the mucoid cell of the gastric glands as first suggested by Lim). This cholinergic discharge releases gastrin."

The mechanism has been further elucidated by Lim and Mozer[19] who showed that gastrin was liberated from the pyloric mucosa by mechanical and

"chemical" stimuli when connected only with Meissner's plexus, the myenteric plexus having been removed. The "chemical" stimuli that they used were not the food products usually referred to as chemical stimuli but cholinergic drugs and histamine. Cocaine, tetraethylammonium and atropine inhibited the response to mechanical stimulation. The action of the cholinergic drugs was prevented only by atropine, indicating, as was to be expected, that they acted directly on the effector cells. The authors conclude that a local reflex mechanism, probably resident in Meissner's plexus, is involved in the release of gastrin. This may be an axone reflex or a synaptic mechanism, probably the latter since it is blocked by tetraethylammonium. The reflex is referred to by the authors as the "adenteric reflex".

The Theory of Uvnas

The observations mentioned previously lead to the conclusion that the cholinergic mechanism involved in the release of gastrin from the pyloric mucosa, in all probability, includes Meissner's plexus. Since this plexus comprises a part of the vagus pathway it is reasonable to inquire whether stimulation of the vagi may not also release gastrin. The idea that vagus stimulation has this effect comprises the first part of the theory proposed by Uvnäs[13]; the second part of this theory holds that neither gastrin alone nor vagus impulses alone can stimulate the gastric glands to secrete HCl but that the two must act together. Even though this theory comprises two distinct ideas, the evidence is of such a nature that they have to be considered together. Uvnäs[13] using a cross circulation technic in dogs showed that on stimulation of the vagi a chemical agent was released into the venous blood draining from the antrum of one animal which augmented the effect on the gastric glands of vagus stimulation in another dog. This agent, he believed, was gastrin. In simpler experiments on individual animals (cats) he found that removal of the pyloric part of the stomach, or ligation of the arteries or veins supplying this region, or cocainization of the pyloric mucosa resulted in failure of the response of the fundic glands to vagus stimulation.

Babkin and his co-workers[20] criticized these experiments and were able to show that under certain conditions the vagus was still effective after removal of the pyloric antrum. They expressed the opinion that failure of the gastric glands to secrete in Uvnäs' experiments was due to inhibition caused by sympathetic stimulation associated with the trauma of the operation, commonly referred to as the "shock" of the operation. A more recent study by Linde[9] clarifies the conflicting data and, except for quantitative differences, confirms Uvnäs' conclusions. Linde showed that shortly after removing the pyloric part of the stomach, the vagus does indeed lose its effect on gastric secretion but if one waits several hours for the shock of the operation to pass off, then some effect can be obtained on stimulation of the vagi. This effect, however, is always less than when the pyloric portion is intact. He also found that ligation of the pyloric arteries greatly reduces the response to vagus stimulation whereas ligation of arteries supplying other parts of the stomach has no such effect. He points out, quite correctly,

that the factor of shock should be as great in the one case as in the other. He noted, as did Uvnäs, that cocainization of the pyloric mucosa had about the same effect as ligation of the arteries.

It will be recalled that excision of the pyloric antrum decreases the acid secretion in response to sham feeding in dogs[16]. Glass and Wolf[21] have recently shown that it likewise reduces the response to insulin hypoglycemia in humans; both, of course, are examples of central vagus stimulation.

Each of the experiments described has a bearing on both aspects of the Uvnäs theory. It is assumed that the interference with the antrum merely eliminates the source of gastrin and that this loss is responsible for the change in the response of the fundic glands to vagus stimulation; but the gastrin mechanism can have no effect unless gastrin is being released, hence the inference that vagus stimulation releases gastrin. The marked depression of the response to vagus stimulation in the absence of the gastrin mechanism indicates that gastrin is essential for a normal response. The argument is weakest where it applies to the mechanism of gastrin release. There is no positive proof that a normal antrum, even in the absence of specific stimulation, may not release enough gastrin to support the response of the fundic glands to vagus stimulation, but the experiments of Dragstedt and his co-workers[22], indicating that exteriorization of the antrum is equivalent to surgical removal, is suggestive.

Further support of Uvnäs' theory, as modified by Linde, is provided by some additional experiments by Lim and Mozer[23]. They prepared animals with three gastric pouches, a vagus innervated pyloric pouch and two fundic pouches, one of which was innervated and the other denervated. When the animals were sham fed only the innervated fundic pouch secreted. The secretion lasted for about 3 hours. This secretion was suppressed when the pyloric pouch was cocainized during the second or third thirty minute period. They concluded that the innervated pouch secreted in response to direct vagal stimulation during the first thirty to sixty minutes but the prolonged secretion was in part due to gastrin released from the pyloric pouch by impulses passing over the vagi.

The Question of the Denervated Pouch

Failure of the denervated pouch to secrete calls for some comment, particularly since it accords with the previous observation of Jemerin, Hollander and Weinstein[24] that neither sham feeding nor insulin hypoglycemia induced secretion in vagus denervated pouches in dogs. These experiments in no way reflect upon the theory that gastrin is important for the secretory response of the gastric glands to stimulation of the vagi but they do raise a question regarding the effectiveness of the vagi in releasing gastrin from the pyloric mucosa; it would appear that if gastrin is released the denervated pouch should also secrete.

Lim's[23] animals had three gastric pouches and an esophagostomy. It may be that with this extensive surgery they were not ideal animals on which to make

a crucial test of the effects of sham feeding on a denervated pouch. Jemerin[24] and his co-workers did not use the classical sham feeding technic* but merely teased the animals with food. It is possible that sham feeding with an esophagostomy would have been a stronger stimulus. With regard to the experiments with insulin, Quigley and Solomon[25] have shown that insulin hypoglycemia causes inhibition of motility in the vagus denervated stomach. Whether it inhibits secretion as well is not known but the possibility should be considered. Even so Schofield[26] has reported that a small amount of secretion may be obtained from a Heidenhain pouch with insulin hypoglycemia. One of his animals also secreted in response to the sight and smell of food. Granted that the secretion so obtained is negligible and probably due to residual parasympathetic innervation the results are still consistent with Uvnäs' original theory. According to him both the presence of gastrin and vagus stimulation are necessary to initiate secretion by the gastric glands. In the denervated pouch one factor is missing, namely the vagus impulses, hence no secretion would be expected. Uvnäs' conclusions, however, have had to be modified, at least quantitatively; hence the explanation becomes more involved.

Although it has, apparently, been proved that either vagus stimulation alone or gastrin alone can induce gastric secretion it will be recalled that the amounts of acid secretion obtained are small and not comparable to the abundant secretion that is elicited when both stimuli act together. Uvnäs[13] and Linde[21] both agree that the effect of gastrin and of vagus stimulation (acetylcholine release) are not merely additive but are truly synergistic, that is, the effect of the two acting simultaneously far exceeds the sum of the effects obtained when each is acting alone. In this connection one should mention the experiments of Langlois and Grossman[27] who found that the gastric secretory response to urecholine was decreased by about 90 per cent (i.e., to about 1/10 of normal) by surgical removal of a previously prepared pyloric pouch.

As a corrollary to these considerations it may be inferred that the minimal effective dose of gastrin will be much greater in the absence of the vagus innervation than in normal circumstances. If a denervated pouch fails to secrete even though the vagi to the antrum may be causing release of gastrin, it may be because the amount of gastrin released in this way is less than the relatively large amount needed to excite denervated glands. Reverting to our original concept of the vagi as serving mainly to augment or inhibit local reflexes it is not unreasonable to infer that when acting alone the vagi will be much less effective than when they are able to facilitate the response to local stimuli; such stimuli are, of course, absent in the experiments with insulin and with sham feeding.

*Since this paper was submitted Dr. Hollander has called my attention to the fact that certain of their animals had an esophagostomy and were sham fed in the classical manner of Pavlov, and were so reported. In these animals, like the others, there was no secretion from the denervated pouch.

Correlation

Investigators necessarily present their new facts and ideas individually, each as a separate study leading to certain conclusions and it is in this way that we have been considering them; but physiology does not consist of unrelated facts. It will help us to see the correlation if we are able to integrate the theories presented into a description of gastric digestion as it occurs normally following an ordinary meal. We may assume that the act of eating initiates the cephalic phase, which at first is entirely dependent on impulses descending over the vagus nerves. These impulses activate the gastric glands either without the aid of gastrin or with the aid of minimal amounts of gastrin that may be present, even in the fasting state. At the same time they impinge upon the antrum where they increase the irritability of the local reflex mechanism involved in the release of gastrin. Perhaps some gastrin is released which may then further augment the effect of the vagi on the gastric glands. In any event, food eventually reaches the antrum and makes contact with the mucosa. Through chemical and mechanical stimulation by the food the local reflex mechanism is further excited causing the release of increasing amounts of gastrin which further excites the fundic glands. Perhaps by this time the initial vagus excitation has subsided somewhat so that the chief dependence is on the gastrin mechanism, but not without some residual augmentation through the vagi. At some point in the process an intestinal phase intervenes but we are still in the dark as to the manner in which intestinal stimuli have their effect.

With this concept we are able also to interpret more clearly some of the effects of gastric surgery. The operation of partial gastrectomy, for example, was designed primarily to suppress the gastric phase of gastric secretion, but experience shows that it also depresses the cephalic phase. The evidence that gastrin contributes substantially to the cephalic phase gives us, for the first time, a satisfactory explanation for this phenomenon. On the other hand, vagotomy was designed as an operation to eliminate the cephalic phase of secretion but it proved also to depress the gastric phase. This is explainable on the assumption that the vagi convey impulses that augment the release of gastrin and also act synergistically with whatever gastrin may be present.

So far in this discussion the most obvious interpretation of the facts has been presented without reference to alternative explanations. It should be pointed out that in this difficult field few experiments are conclusive and no interpretation is final in the sense that all alternative theories are excluded. Even so, it is evident that the physiology of secretory nerves and hormones has entered a new phase which promises to be much more productive than the phase that is passing. The new evidence relates almost exclusively to the control of gastric secretion but similar problems arise in connection with pancreatic secretion, intestinal secretion, the biliary tract and, indeed in every situation in which both nerves and hormones are involved in the regulatory process.

Summary

The experimental evidence reviewed indicates that:

1. Gastrin is released from the pyloric mucosa by local mechanical and chemical stimuli acting through a cholinergic nervous mechanism that probably comprises Meissner's plexus and its local and central connections.

2. Stimulation of the vagi facilitates the nervous mechanism involved in the release of gastrin and may cause the release of some gastrin in the absence of specific local stimuli.

3. Neither gastrin alone nor vagus stimulation alone can cause maximal stimulation of the gastric glands to secrete HCl. Abundant secretion is obtainable only when nervous and hormonal stimuli act simultaneously.

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Discussion

Dr. Franklin Hollander (New York, N. Y.):—Dr. Thomas has presented to us this afternoon a most lucid analysis of the various mechanisms by which gastric secretion is normally stimulated. May I first of all point out, without going

into details, that Dr. Janowitz and I recently reexamined some data previously published by Jemerin, Weinstein and myself (in the paper referred to by Dr. Thomas) and derived what appears to be excellent evidence to demonstrate that the vagi are not involved in the elaboration of gastrin by the pyloric antrum. This is contrary to some of Dr. Thomas' story, but I will discuss it with him later rather than take time for it now. In the time allotted me for discussion, I should like to present a matter which may be of a little more immediate interest to you, as clinicians.

It is obvious that all of our thinking about the etiology and the therapy of peptic ulcer and allied gastric disorders is concerned with the reduction or elimination of hydrochloric acid secretion. To this end, of course, we employ various chemical devices for neutralizing the acid and for inactivating the pepsin. Beyond this, however, all of our efforts have been designed in accordance with the ideas just discussed by Dr. Thomas, and are directed toward intercepting one or two of the modes of stimulation which he described. Since none of these has been truly successful in completely eliminating this hydrochloric acid secretion up to the present time, my own thinking on this problem for some years past has gone in a different direction.

I have been looking for what Dr. Alvarez some years ago designated a monkey wrench which can be thrown into the machinery of hydrochloric acid formation, and it is this line of thought which I want to tell you about.

A diagrammatic representation of parietal cells is familiar to all of you. Now, all of the various mechanisms for ulcer therapy which we are using at the present time are either pharmacological or surgical, and therefore operate external to the cells; that is, we try to cut the neural innervation, or block it with anticholinergic agents, or eliminate the hormonal stimulation of these parietal cells. If, however, we could throw a monkey wrench into the machinery inside this cell, the machinery which is intimately concerned with making the hydrochloric acid, we would finally have evolved that long-sought-for ideal medical therapy which would make the activities of the surgeons in this regard wholly unnecessary.

Our success in this direction has been nil until within the last year. In order to find such a monkey wrench, I have tried, first of all, to discover how the hydrochloric acid is being made inside the cell. The little intracellular canaliculus is really a collecting device for the acid secretion as it is first poured out of the cell; the fluid then travels on through the intracellular canal to the main collecting tube of the gland and thence into the gastric cavity. The walls of the canaliculus possess some thickness. Now without going into great detail on this question, we gradually evolved this picture of hydrochloric acid formation. It is made by hydrolysis of sodium and potassium chlorides brought to the parietal cells from the blood stream by the interstitial fluid. Through the canalicular wall hydrogen ion from water goes out along with chloride ion that comes

from the interstitial fluid, and thus emerges as the hydrochloric acid of the parietal secretion. The corresponding hydroxyl ion from the water passes back into the interior of the cell where it is neutralized immediately; otherwise it would kill the cell in short order.

Hence, a large part of parietal cell function is concerned with a mechanism for effecting this neutralization and removing this waste product. These neutralizing agents, in small degree, are phosphate buffer from the interstitial fluid, and lactate buffer which arises from lactic acid formed by glycolysis within the cell. Chiefly, however, it is the carbonic acid-bicarbonate buffer which exercises such intracellular neutralization, and this is formed by several routes: first, from carbon dioxide coming from outside the cell, and secondly, from carbon dioxide which is derived by oxidation within the cell. Regardless of the source, this CO_2 combines with water to form carbonic acid (which neutralizes the hydroxide and is carried away as alkali bicarbonate in the blood stream). Now, back in 1939, Davenport demonstrated that the enzyme, carbonic anhydrase, is present within the parietal cell. That being the case, he and everybody else working in this field felt that carbonic anhydrase plays an important role in speeding up the rate of carbonic acid formation and neutralizing this hydroxyl ion. Unfortunately, all the data Davenport (and several other workers following him) could gather could not prove that this enzyme actually functions in this way. As a result, Davenport finally retracted his theory regarding its function in gastric secretion.

During the last year, however, Drs. Janowitz and Colcher, and I have been able to demonstrate that Davenport's theory is actually correct. It happened in this way: Dr. Roblin of the American Cyanamid Company, and some of his associates, synthesized a number of compounds which are known to inhibit carbon anhydrase in the test tube. Some such compounds (e.g., sulfanilamide) are ineffective as regards interfering with gastric secretion *in vivo,* presumably because they are not powerful enough. One of these new compounds, however, (Diamox, #6063) is 440 times as powerful as sulfanilamide itself, and so we decided to try it out on living animals with Heidenhain pouches in which the gastric secretion was stimulated with histamine. To our great delight, we found that Diamox is actually able to block the formation of hydrochloric acid in the living animal. In other words, we had here finally a monkey wrench which could be thrown inside the parietal cell to interfere with its machinery. The maximum inhibition of acid formation we could get was 97 per cent, most of the experiments showing 80 to 97 per cent regardless of dosage. From the chemistry of HCl formation as I have described here, there is reason to suspect that a greater degree of inhibition, i.e., complete blockage, is not possible. Whether this is so or not remains for further experiments to determine.

The action of this drug on man is already being investigated. As yet we have no results to report to you because of its toxicity, which may prove an

insurmountable barrier. Whether this is the case or not, we are confident that finally we are on the track of the long-sought monkey wrench. If it doesn't operate by interference with the carbonic anhydrase mechanism it will be by interference with some other enzyme which functions within the parietal cell, possibly even one of the enzymes concerned with metabolic processes in the powerhouse that gives rise to lactic acid and the energy for secretion.

THE GENERAL ADAPTATION SYNDROME (G-A-S) AND GASTROENTEROLOGY*

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It would be impossible to present before your association a well balanced and fairly complete outline of the General Adaptation Syndrome and the "adaptive hormones" (such as ACTH, STH, the corticoids), besides this would hardly be necessary since we had already done so in a series of books on Stress[1-4].

What I should like to undertake during the time limit assigned to me, is to present before you a brief outline of the G-A-S as it affects reactions to topical or systemic injury, and follow this by an outlook concerning the possibilities of this approach to therapy.

In my schematic outline I shall place major emphasis upon the effects of stress and the adaptive hormones upon the process of inflammation, since in so many gastrointestinal diseases it is precisely in this respect that the G-A-S assumes importance.

Brief Outline of G-A-S Mechanism

To summarize the most relevant aspects of the G-A-S, we might say that all agents which act upon the body or any of its parts exert dual effects:

1. *Specific actions*, with which we are not concerned in this study, except insofar as they modify the nonspecific actions of the same agents.

2. *Nonspecific or stressor effects*, whose principal pathways (as far as we know them today) are illustrated in the accompanying drawing.

The *stressor* acts upon the *target* (the body or some part of it) directly (thick arrow) and indirectly through the pituitary and adrenal.

Through some *unknown pathway* (labelled by a question mark), a stimulus travels from the directly injured target area to the *anterior pituitary*. It notifies the latter that a condition of stress exists and thus induces it to discharge ACTH.

It is quite possible that this "first mediator" of hormonal defense is not always the same. In some instances, it may be an adrenalin discharge, in others a liberation of histamine-like toxic tissue metabolites, a nervous impulse or even a sudden deficiency in some vitally important body constituent (such as glucose or an enzyme).

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ACTH stimulates the *adrenal cortex* to discharge corticoids. Some of these, the *prophlogistic corticoids* (P-C), stimulate the proliferative ability and reactivity of connective tissue; they enhance the "inflammatory potential". Thus, they help to put up a strong barricade of connective tissue through which the body is protected against further invasion by the pathogenic stressor agent.

Under ordinary conditions, however, ACTH stimulates the adrenal much more effectively to secrete *antiphlogistic corticoids* (A-C). These inhibit the ability of the body to put up granulomatous barricades in the path of the invader; in fact, they tend to cause involution of connective tissue with a pronounced depression of the inflammatory potential. Thus they open the way to the spreading of infection.

As far as we know, ACTH always stimulates the adrenal to produce the various corticoids in the same proportion and always with a great predominance of A-Cs. The *somatotrophic hormone* (STH) of the pituitary, however, also increases the inflammatory potential of connective tissue, somewhat as the P-Cs do; hence, it sensitizes the target area to the actions of the latter.

It is possible that the hypophysis also secretes some special corticotrophin which induces the adrenal to elaborate predominantly P-Cs; indeed, STH itself may possess such effects, but this has not yet been proven. In any event, if ACTH were the only corticotrophin, the actions of the corticoids produced under its influence can be vastly different, depending upon "conditioning factors" (such as STH), which specifically sensitize the target area for one or the other type of corticoid action. Actually, conditioning factors could even alter the response to ACTH of the adrenal cortex itself, so that its cells would produce more A-Cs or P-Cs. Thus, during stress, one or the other type of effect can predominate.

The fundamental reaction-pattern to topical stressors is "inflammation", to systemic stressors, the "G-A-S". Various combinations of these two basic responses constitute the essence of most diseases.

Outlook Concerning the Future of Stress Research

During the past year, perhaps the most important contribution to our understanding of stress and of the adaptive hormones was the growing realization of the limitations of ACTH and A-C therapy. When ACTH and cortisone were first introduced into clinical medicine, there was much hope that treatment with these hormones might cure a large number of hitherto incurable diseases; indeed, it was felt that these drugs (and they were considered as merely pharmacologic agents, which means drugs) would have such a wide spectrum of practical application that they would "revolutionize medicine". These hopes did not materialize. The practical value of antiphlogistic hormone treatment, as it is now practised, is limited by its undesirable side-effects and many experienced clinicians recommend that they not be used routinely even in the treatment of rheumatoid arthritis where they were supposed to be most useful[5-7]. They will

continue, of course, to be valuable additions to our therapeutic armamentarium. This is true particularly in the treatment of certain inflammatory diseases of the eye, which do not tend to recur soon after discontinuation of treatment, or can be controlled by the purely local application of A-Cs, without introducing the danger of systemic complications. But, with such drastic limitation, the clinical use of these hormones would be a poor return for the untiring efforts of all those investigators who studied the mechanism of response to stress with the hope of finding a new avenue to the effective treatment of disease in general.

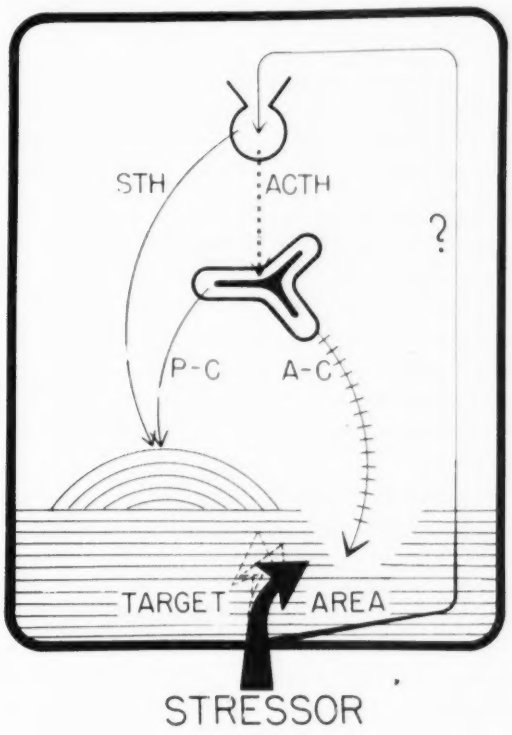

Fig. 1

Although we have not yet learned how to use adaptive hormones effiiciently in the treatment of systemic diseases, without producing overdosage effects, the body itself knows this secret. To take but one striking example in the course of exposure to severe stress, the human organism can apparently produce effective amounts of antiphlogistic hormones (e.g., during pregnancy, starvation and other types of stress) without eliciting any serious manifestations of hormone overdosage. It accomplishes this presumably by appropriate compensatory reactions

which condition the response to these hormones. We believe, therefore, that the real future of this field lies not in the merely empiric gathering of data concerning the value of adaptive hormones in this or that disease, unguided by any theory, but in the systematic investigation of the total integrated response to stress.

Pasteur and his contemporaries introduced the concept of specificity into medicine, a concept which proved to be of the greatest heuristic value up to the present time. Each individual well defined disease, they held, has its own specific cause. It has been claimed by many that Pasteur failed to recognize the importance of the "terrain", being too preoccupied with the pathogen (microorganism) itself. This is incorrect. His work on induced immunity shows how clearly he realized the importance of the "terrain". The theory which directed the most fruitful investigations of Pasteur and his followers was that the organism can develop specific adaptive reactions against individual pathogens and that by imitating and complementing these, whenever they are short of optimal, we can treat many of the diseases which are due to specific pathogens.

To our mind, the G-A-S represents, in a sense, the negative counterpart, or mirror image, of this concept. It holds that many diseases have no single cause, no specific pathogen, but are largely due to nonspecific stress, and to pathogenic situations which result from inappropriate responses to such nonspecific stress.

Hence, if in closing this "outlook" we may venture a prediction, we would like to reiterate our opinion that *research on stress will be most fruitful if it is guided by the theory that we must learn to imitate—and if necessary to correct and complement—the body's own autopharmacologic efforts to combat the stress factor in disease.*

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Discussion

Dr. Flanders Dunbar (New York, N. Y.):—I hope that you all have enjoyed Dr. Selye's paper as much as I have. Unfortunately, I did not receive it in time to read it before I thought about what I wanted to say; nevertheless, I think that Dr. Selye, like all of us, is interested in stress and has attempted to define the general range of adaptation to stress. Clinicians watch for stress in signs of muscle tension. We usually blame everything on muscle tension without defining what we mean by muscle tension, but we know very well that there are all kinds of tension.

I think Dr. Selye believes that the means of adaptation at the disposal of any individual are limited by his personality type. What is more important is that the patient's defenses against adaptation have a bearing on the nature of physiologic dysfunction occasioned by stress, and on the type of somatic change which may ensue.

Dr. Selye has pointed out that derailments of the general adaptation syndrome may participate in the production of duodenal ulcer. Gastric erosions frequently accompany an alarm reaction but often one can have the alarm reaction and no gastric erosion. Similarly, different individuals react differently to ACTH and to any kind of drug that we may want to give them.

Lindeman, Alexander Wolf, and many others have attempted to determine just why the gastrointestinal tract becomes a target organ in some persons but not in others subjected to similar stress. Whatever the hormonal type, the person for whom the gastrointestinal tract has become the target organ is likely to show abnormal responses even extending to related organs and organ systems; hence diverse illness syndromes may be precipitated during adaptation to stress. For example, Jules Masserman noted that when monkeys were subjected to conditions producing an experimental neurosis, nine out of ten in one particular experiment would starve themselves to death, whereas a tenth one would overeat and kill himself from over-eating.

Every patient does not have the same reaction to cortisone. Every patient does not have the same reaction to rage. Every patient does not have the same defense against situations that threaten his sense of security.

In my field it is important to understand the patient well enough to be able to predict what type of patient is going to have this or that as a target organ, and also, if possible, to know ahead of time the type of disequilibrium that is likely to result in somatic damage. It happens frequently that patients are discharged from a hospital with the verdict "no demonstrable signs of organic disease," and come back a little later with the very disease for which they were being examined. I remember several during my internship.

One girl who complained of indigestion was studied carefully "from all points of view" over a period of more than a year. Finally it was decided that she just had a neurosis, and she was sent for psychotherapy. I happened to see her for awhile. She improved remarkably, lost her symptoms. Then the clinic was closed for two months in the summer. I wrote a note on the chart suggesting that this patient be followed in the medical clinic carefully because she had the type of personality that suggested that ulcer might happen at any time. She seemed to have "ulcer personality". I also instructed the patient to come back if there was any recurrence of symptoms. She did come. The clinic was still closed, but she was sent to the neurological clinic and given sedatives for sleeplessness. About three weeks later the clinic was open and there was a letter on the desk from this patient saying, "I have been in Such-and-Such Hospital for the last

three weeks. I have had three transfusions for hemorrhage from an ulcer in my stomach. If that is what you were treating me for, why didn't you tell me?"

She had been very carefully studied and there were no signs of ulcer. The only discovered sign of the fact that an ulcer was brewing was her particular personality type and manner of behavior.

Every mammalian (and perhaps even organisms farther back on the ladder of evolution) has an Achilles heel. Within the human being, it is particularly important to discover what the vulnerable point will be when stress becomes too great for equilibrium to be maintained. Some persons under stress fill up with gas, some people get spasm of the capillaries—whatever the words, whatever the concept, the point of greatest vulnerability for each individual under stress should be discovered if medicine is to be preventive and not merely curative.

The field Dr. Selye presented this morning needs further definition, and I should like very much to say something in closing the discussion, about its relationship to different personality types.

I think that patients, as a result of their experience and of their conditioned reflex behavior, starting from very early may shift the balance in their hormonal system all on their own. Then it is our job to notice what the patient is doing and to ascertain whether it can be prevented or corrected.

Research is progressing and new observations are being tested. The facts already known may be better applied, and I think it should be remembered that it is less difficult to discover something new than to make adequate application of what is already known. I hope all of us will continue to apply Dr. Selye's observations relative to the general adaptation syndrome.

Dr. Hans Selye (*Montreal, P. Q.*):—I should like to thank Dr. Dunbar for her remarks, which touch upon rather interesting implications of the G-A-S concept. It is certainly my impression that psychological conditions may at times predispose the individual's reaction to stress and, in turn, certain "conditioning factors" (e.g., heredity, diet) inherent in the individual, may alter its response to an emotional stress.

It is my impression that, under certain conditions, stress producing emotional upsets can lead to a sort of conditioned reflex, which results in an abnormal hormonal response. It is conceivable that, after prolonged exposure to the same kind of psychologic strain, an individual develops the "habit" to react to it by an excess of STH or prophlogistic corticoids, so that the emotional stress itself elicits manifestations similar to those normally caused by hormone overdosage. If in such an individual some drastic procedure, for instance shock therapy, rectifies the reaction, one may assume that the intense new kind of stress represented by the therapeutic agent, somewhat shakes the organism out of the pre-established abnormal path or pathogenic "conditioned reflex" and, thus, re-establishes normalcy.

THE INCIDENCE OF THE COEXISTENCE OF GASTRIC ULCER IN ESOPHAGEAL HIATUS HERNIA OF THE STOMACH*

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and

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Although numerous valuable contributions have been made to our knowledge of hiatus hernia, there have been few reports in the literature in which attention has been focused on the coexistence of gastric ulcer with this condition. In a perusal of the literature there have been a number of single case reports of the association of gastric ulcer with hiatus hernia, and other reports recorded in which the coexistence is mentioned in statistical studies.

Hiatus hernia of the stomach may be associated with many pathologic conditions, few of which have any direct relationship to the hernia. One of the commonest findings in hiatus hernia is the presence of anemia, which occurs in a high percentage of cases. The anemia is attributable to loss of blood accounted for either by congestion and/or erosion of the gastric or esophageal mucosa, or the result of a complication such as esophageal or gastric ulcer or malignancy. Bleeding as a symptom of this condition is probably caused more often by congestion than any of the other conditions mentioned.

In this presentation an attempt was made to collect from the literature all reported cases of hiatus hernia associated with gastric ulcer. In some of these reports no specific mention was made as to the location of the ulcer, merely stating peptic ulcer. For obvious reasons these were omitted since many of the peptic ulcers were situated in the duodenum. In addition, there were a number of reports intermingled with other studies as well as some case reports not available. The cases studied here were compiled from roentgenologic, surgical and autopsy material. Only those cases with a chronic gastric ulceration were considered. The acute ulcers and mucosal erosions of the stomach were eliminated from this study.

The purpose of this presentation is threefold. (1) to establish the true incidence of the coexistence of gastric ulcer with hiatus hernia. (2) To determine whether the hiatus hernia per se is a causative factor in the development of gastric ulcer. (3) To compare the incidence of the coexistence of gastric ulcer in hiatus hernia with the incidence in the general population.

The incidence of gastric ulcer associated with hiatus hernia of the stomach has not been fully established. The incidence of gastric ulcer coexisting with a hiatus hernia while admittedly not too common, occurs perhaps more frequently

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than hitherto credited. In order to determine the incidence a review of the literature was made. In a collected series of 599 cases of hiatus hernia,[1-5,8,10-15,17-29,31-40] there were twenty-four cases associated with a gastric ulcer, an incidence of 4 per cent. In a study of 110 cases of hiatus hernia in our series there were five cases with gastric ulceration, or an incidence of 4.5 per cent. In addition to the above there were forty-three cases reported in the literature, making a total of seventy-two cases in which there was a coexisting gastric ulcer with a hiatus hernia of the stomach recorded up to 1952. As already mentioned, there is no doubt that there are many other cases reported in the literature which for many reasons could not be found.

It must be pointed out that the autopsy and surgical incidence of hiatus hernia do not reveal the true incidence. My own experience (M. F.) indicates that the roentgen examination has consistently given more accurate information of this condition.

The significance of the incidence of gastric ulcer as a complication of hiatus hernia must be studied against the background of the etiologic factor responsible for the production of the ulceration. The question has often arisen whether a hiatus hernia predisposes to the development of an ulcer on the lesser curvature in the hiatal isthmus between the herniated and abdominal segments of the stomach as a result of friction, constriction, congestion and irritations to which the mucous membrane is prone. In order to study this phase it might be well to compare the incidence of gastric ulcer in the normal population with that found in cases with hiatus hernia. In 4,000 autopsies Hurst and Stewart[16] found 194 cases of gastric ulcer, an incidence of 4.85 per cent. Portis and Jaffe[30] in 9,171 autopsies found 185 cases of gastric ulcer, an incidence of 2 per cent. In 1,082 autopsies we found twenty-five gastric ulcers, an incidence of 2.3 per cent[7]. Since it is generally known that the autopsy incidence of gastric ulcer is not the true incidence, because of the fact that many ulcers heal during the lifetime of the patient without leaving any demonstrable gross signs of the presence of the ulcer, we and also others have pointed out this phenomenon in ulcer cases, that the incidence of gastric ulcer is greater than found at autopsy.

Contrary to prevailing opinion that in hiatus hernia the constant irritation of the gastric mucosa due to compression and friction of the stomach through the esophageal hiatus of the diaphragm may be a factor in the production of a gastric ulcer, this study does not permit this conclusion. The percentage-wise difference is not statistically significant.

Although the etiology of gastric ulcer is unknown, it is believed by some that trauma as a result of sliding of the stomach through the constricted channel of the esophageal hiatus probably plays some role in the etiology of ulcers associated with hiatus hernia. It would seem that the trauma engendered from the sliding variety of hernia over a long period of time is sufficient to produce this complication or at least to initiate it by the constant irritation. If this were

true, gastric ulcers would not often be seen in the nonsliding type and in those cases with short esophagus. It can be stated here that gastric ulcers are observed in both the sliding and nonsliding hiatal hernias.

In our 110 cases of hiatus hernia there were ninety-three of the sliding variety, seventeen were fixed, and in seven there was a short esophagus. The size of the herniated segment of stomach varied. In our 110 cases, ninety-four were small and sixteen were large. The gastric ulcer may occur in any portion of the stomach, on the lesser and greater curvatures or walls. It is most often seen on the lesser curvature. The site of the gastric ulcer in relation to the diaphragmatic hiatal opening is divided accordingly into (1) the herniated segment of stomach situated above the diaphragm or intrathoracic, (2) situated in the isthmus between the thorax and abdomen, or on the level of the diaphragm constriction, and (3) situated below the diaphragm. Of the seventy-two cases there were fifty-eight which mentioned the site of the gastric ulcer. It occurred in the herniated intrathoracic segment twenty-seven times, in the hiatal isthmus or level of the diaphragm in eleven, and below the diaphragm in twenty cases.

The size of the gastric ulcer was not often mentioned in the records of the collected cases. It has been noted that these ulcers are often of large size. Whether the larger sized ulcers are more frequently associated with hiatus hernia than usually encountered in non-hernia cases is questionable. In our own five cases the size of the ulcer craters as demonstrated roentgenologically was no larger than those noted in non-herniae.

It is interesting to point out that the vast majority of hiatus hernia cases occur in females. Feldman[6] found that approximately 75 per cent occur in females. The incidence of females with coexistence of gastric ulcer and hiatus hernia must necessarily be high. All of our five cases were females. The majority of the collected cases also occurred in females.

In our 110 cases of hiatus hernia diagnosed by roentgenologic examination both the hernia and the gastric ulcer were well demonstrated, i.e., the herniated stomach and the gastric ulcer niche. The roentgen diagnosis seems to be adequate to sustain the diagnosis of the two conditions and is the best means to determine the incidence. For obvious reasons this examination far surpasses both surgical and autopsy procedures for the study of these conditions.

It must be emphasized that the gastric ulcer cannot always be demonstrated by the ordinary methods of roentgen examination. This is due to the position of the ulcer, rotation of the stomach, because of partial volvulus, overshadowing by the redundant herniated segment of stomach, or overshadowing by the diaphragm. In some instances the ulcer may occur in the hypertrophied folds within the herniated segment of the stomach. This gives the appearance of a localized opacity within the mucosal folds, and thus the ulcer crater is misinterpreted. Since most of the ulcers are located on the lesser curvature of the stomach, their disclosure in most instances is readily detected.

Perforation has been reported to occur as a result of necrosis, pressure and thinning out of the gastric wall, and rupture following incarceration of the herniated segment of the stomach. More often, however, the perforation is due primarily to the chronic gastric ulceration. Of the seventy-two cases there were eight reported to have perforated; four of these perforated into the lesser peritoneal sac. The 50 per cent incidence of lesser peritoneal cavity perforation is highly significant. It appears that lesser sac perforations occur more frequently in perforation of gastric ulcer associated with hiatus hernia than in the non-hernia cases.

Healing of the gastric ulcer may occur under medical management. Healing has been observed in many instances. Scarring of a previously diagnosed chronic gastric ulcer in hiatal hernia has been observed in some instances at operation and at autopsy.

Conclusions

1. This report comprises a group of sixty-seven collected cases and five of our own, a total of seventy-two cases of hiatus hernia associated with gastric ulceration.

2. In 709 cases of hiatus hernia there were twenty-nine cases of chronic gastric ulcer, an incidence of 4 per cent.

3. Statistically, the incidence of the existence of gastric ulcer in hiatus hernia is not significantly greater than noted in the general population.

4. Hiatus hernia does not seem to be an etiologic factor in the production of gastric ulcer.

5. The site of the gastric ulcer in fifty-eight cases of hiatus hernia was predominantly on the lesser curvature and occurred in the intrathoracic segment in twenty-seven, in the hiatal isthmus or level of diaphragm in eleven, and below the diaphragm in twenty cases.

6. Of the seventy-two cases of hiatus hernia associated with gastric ulcer eight had perforated; four of these perforated into the lesser peritoneal cavity.

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Discussion

Dr. Joseph A. Shaiken (Milwaukee, Wisc.):—I wonder if Dr. Feldman would tell us if there is special technic in demonstrating these hiatus herniae. I wonder if he could enlighten us on an approach.

Dr. Maurice Feldman (Baltimore, Md.):—The most important part of the x-ray procedure is the care in which examination is made. We have had a number of cases of gastric ulcer associated with hiatus hernia, and others have had, as well, in which the ulcer has been misinterpreted by the fact that the ulcer apparently was located on the posterior wall, and it was not recognized until some complication occurred, such as, perforation or hemorrhage. I think it is a question of experience, and as I brought out in my paper, very often there are accumulations of barium in the mucosal folds which are misinterpreted as an ulcer niche.

There is no special or particular method that roentgenologists have except for the care in which the examination should be made. Often by examining the patient in the Trendelenburg position, we are enabled to fill the cardiac end of the stomach and, therefore, one is more likely to find the ulcer crater.

I should like to make a few remarks to emphasize the importance of making certain that the esophagus is long enough to reach into the abdomen in all cases before surgery is contemplated. We have had a few cases—and I have seen a number of others in which after operation the hernia still remained. It is very important to be sure that the esophagus is long enough to reach into the abdomen, otherwise there will be no surgical cure.

We believe, as Dr. Farrand has mentioned, that the vast majority of cases are asymptomatic and that no surgery is required. It is only those that have complications where surgery is indicated.

Allison, many years ago, directed our attention to the fact that the shortening of the esophagus is often due to cicatricial changes following ulceration of the esophagus.

Another point I should like to make is that we have also made a study of the association of carcinoma with hiatus hernia, and in that study we have likewise noted that there is no greater incidence of carcinoma among cases with hiatus hernia.

It has been my intention here in presenting this topic, to add further to our basic knowledge of the association of conditions relating to hiatus hernia. It has been hypothetically assumed by many that gastric ulcer is a common complication of hiatus hernia.

We have shown in our present study that the incidence is not any more common in hiatus hernia than in the known population. Furthermore, it is well known that the incidence of bleeding is exceptionally high in hiatus hernia cases. As I brought out, this is due in most instances to congestion. I should like to further emphasize that in every case of bleeding, notwithstanding the fact that peptic ulcer is the most common cause, it is still very important to look for the presence of a hiatus hernia to account for the bleeding.

Dr. Samuel Morein (Providence, R. I.):—During the past twenty-eight years, I have observed about one hundred cases of diaphragmatic hernia in a series of about 10,000 gastrointestinal x-ray examinations, or an incidence of about one per cent. In this series the incidence of the existence of a gastric ulcer in a herniated portion of the stomach was approximately the same as Dr. Feldman's findings. Another interesting finding in my series of cases was carcinoma which developed at the site of a gastric ulcer within the hiatus hernia. This occurred in two per cent of the total series. In one such case observed, this occurred on the greater curvature of the stomach in a woman of over seventy. Again it occurred in a man with a gastric ulcer observed over a period of several years.

I should like to ask Dr. Feldman a question. Because of the fact that the herniated portion of the stomach is within the chest cavity and therefore is not as accessible as the lower portion of the stomach, isn't it possible that by our present technic we are not able to detect ulceration as frequently as the symptomatology suggests in diaphragmatic hernia?

In my series hematemesis or bleeding occurred in nearly fifty per cent of the cases. On the other hand, ulceration occurred in less than ten per cent of the series.

Dr. Maurice Feldman:—With our present methods of roentgen examination of the stomach, utilizing the compression technic for mucosal studies, one is better able to visualize the interior of the stomach. When one completely fills the stomach with barium, there is an overshadowing of structures and, therefore, one is likely to miss the presence of an ulcer.

To answer Dr. Morein's question, ordinarily in examining the stomach we use the compression technic as a means of spreading the barium. in order to demonstrate the mucosal folds. When part of the stomach is situated in the chest, one cannot use compression adequately. Fortunately, most cases of hiatus hernia are not of the fixed type. They slide back and forth into the stomach, and, therefore, we are able to manipulate the stomach and visualize the folds. On the other hand, the cardiac end normally is difficult to manipulate and that is one of the

reasons why it is important to make your mucosal studies before filling the entire stomach. In other words, after the first mouthful of barium is swallowed, that is the time when one elicits important findings, because if you overload the stomach, you are going to miss the early and obscured lesions.

Dr. Hyman I. Goldstein (Camden, N. J.):—I should like to ask my keen-eyed roengenologist friend Dr. Feldman the question, that since in these 72 cases he listed, of ulcer, he mentioned "extra trauma", whether he has met with any cases in the literature, or in his series of 72, *of malignant change because of* an existing ulcer in a hiatus hernia.

Several hundred years ago Jerome Capivaccius in his *"Practica Medica"*, 1594, Frankfort, Book III: Chapts. IV and V recognized malignant change in ulcer, but I don't know whether he knew about hiatus hernia in this connection!

Peptic ulcer of the *esophagus* was clinically diagnosed by Debove. Albers (1839) early described peptic ulcer of the esophagus and noted its similarity to gastric ulcer. Quincke (1879) of Kiel, Beatrice Russell (1899) and Tileston (1906) reviewed this subject. Humphry (1855) nearly a century ago reported esophageal ulceration following burns. Peptic ulcer of the esophagus was seen esophagoscopically by Starck in 1905, and Barclay (1915). As to hernia of the stomach—this was recorded by M. E. Ettmüller, A. Baraduc (Paris, 1837); P. Kirschbaum (Argentorati, 1794) two hundred years ago! Anseaux (Paris, 1807) P. Bérard, (Paris, 1835) and J. L. Petit (1774, Eventration).

Has Doctor Feldman recently seen cases of *"Sanduhrmagen"* (*"Hour-glass stomach"*)?

Lazarus Riverius, Gerardus Blasius in 1677, Claudius Amyand (1732), Laurentius Heister (1754); J. B. Morgagni (1761); Joseph Lieutand (1703-1780); Ed. Sandifort (1779) and F. Delius (1778) observed instances of *"hour-glass stomach"!*

The development of cancer on ulcer was observed by A. F. Holtzhausen (1832), Peacock (1848), Platow (1877), Dieulafoy (1897), Scott and Mider (April 1938), Hauser (1883), Koch (1893), Letulle (1897), Fenwick (1902), Rokitansky and Dittrich, Leber, Zenker, Rohenheim, Eichhorst, Ewald, Fritz Stromeyer (Freiburg, 1912), Eusterman and others!

ABSTRACTS

LIVER AND BILIARY TRACT

LIVER BLOOD FLOW AND HEPATIC GLUCOSE PRODUCTION: E. B. Hallett, G. W. Holton, J. C. S. Paterson and J. A. Schilling. Surg. Gynec. & Obst. 95:401-406 (Oct.), 1952.

Estimated hepatic blood flow, glucose production, and splanchnic oxygen consumption were recorded in normal dogs and following Eck fistula. The estimated hepatic blood flow before and after splenectomy were recorded. These results appeared inconclusive. A reduction of approximately 50 per cent in the estimated hepatic blood flow occurred following Eck fistula. Glucose production appeared to be unaltered by Eck fistula. The oxygen consumption fell following an Eck fistula in all but one instance in the same range as the reduction in blood flow. This suggested that under the experimental conditions the liver is responsible for approximately one half of the total splanchnic oxygen consumption.

Addendum: Since this paper was submitted for publication, the work of Werner, and Horvath appeared in the J. Clin. Invest.: **31**:433-440, 1952, concerning the measurement of hepatic blood flow in normal dogs with bromsulfalein. Their similar findings in normal animals further emphasize the vagaries of the bromsulfalein method of measurement of liver flow, particularly when nembutal anesthesia is employed with an intact spleen.

J. R. Van Dyne

RELATIONSHIP OF POSTCHOLECYSTECTOMY DISTURBANCES TO BACTERIAL SENSITIVITY: W. K. Jennings, L. R. Ortega and L. Braslow. Surg. Gynec. & Obst. 95:439-445 (Oct.), 1952.

The incidence of surgical failures in a series of 149 cases studied were 28 per cent. A high percentage of unsatisfactory results (45 per cent) was found in patients with a definite clinical history of allergy. The postcholecystectomy syndrome occurs more frequently in patients subjected to cholecystectomy for noncalculous cholecystitis. The incidence of clinical allergy was found to be highest and the percentage of skin reactions toward autogenous vaccines greatest among this group. Evidence was presented to support the postulate that sensitivity to residual bacterial infections may explain certain cases in which the cholecystic syndrome persists after removal of the infected gallbladder.

J. R. Van Dyne

PANCREAS

SURGICAL CONTRAST VISUALIZATION OF THE PANCREATIC DUCTS: Lucien Leger, J. Zerolo and J. Lataste. Arch. mal de l'app. dig. 41:257, 1952.

The difficulties of clinical and surgical diagnosis of pancreatic diseases, particularly carcinoma of the pancreas and chronic pancreatitis, have stimulated the study of this problem.

Studies on the cadaver have convinced the authors of the possibility of catheterizing and injecting the duct of Wirsung. After duodenopancreatic dissection, the duodenal papilla is exposed by vertical duodenotomy performed over the second portion of the duodenum. Catheterization of Wirsung's duct is performed with a special polyethylene tube, 1 mm. in diameter. It is particularly noteworthy that pancreatic catheterization causes the flow of a clear liquid.

It is reassuring to note that the stylet, rubber bougie or polyethylene tube passes more easily into Wirsung's duct than into the common bile duct, though one would be inclined to believe the opposite.

Two to 3 c.c. of 70 per cent diodone is now injected into the pancreatic duct, and a roentgenographic exposure is made.

The polyethylene tube is left *in situ*, in Wirsung's duct, whence it is made to emerge through a tiny gap in the wall of the duodenum which is sutured at two places and attached to the anterior parietal peritoneum. This technic permits obtaining pure pancreatic juice and to study its chemical characteristics and the function of the gland.

The roentgen examinations described can

be repeated several times during the operation, and also on the following days, to verify the position of the polyethylene tube in Wirsung's duct. All patients made good recoveries. Scar formation was in no way retarded.

In chronic pancreatitis the authors observed an image indicating pseudodiverticulum, and more often the dilatation of pancreatic acini, in multiple opaque spots which are not present in case of normal pancreas.

In Vaterian ampulloma, there is a dilatation of the Wirsung duct with a reflux of the opaque medium in the common biliary duct.

In the case of pancreatic carcinoma the Wirsung duct is largely dilated and its edges are irregular.

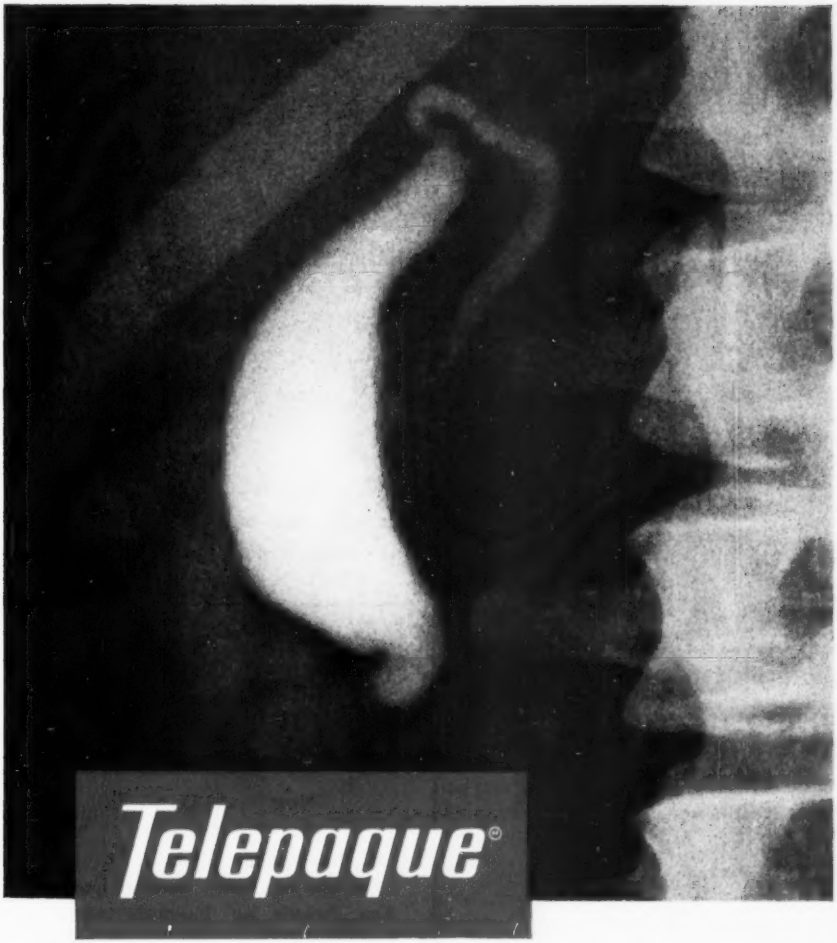
It is noteworthy that pure pancreatic juice, which flows by the polyethylene tube, contains active ferment – and particularly *active trypsine* – instead of trypsinogen as textbooks of physiology teach us.

The reflux pathogenesis in acute hemorragic pancreatitis must be considered again with this new notion.

TECHNICAL CONSIDERATIONS IN RESECTION OF THE HEAD OF THE PANCREAS: E. Brintnall. Surg. Gynec. & Obst. 95:181-183 (Aug.), 1952.

A method for resection of the head of the pancreas is described. The "left to right" mobilization of the pancreatic head appears to make the procedure both simpler and safer. The two which occurred in 18 resections (operative mortality rate 11 per cent) were in patients who would be considered inoperable according to the present criteria of operability.

J. R. VAN DYNE



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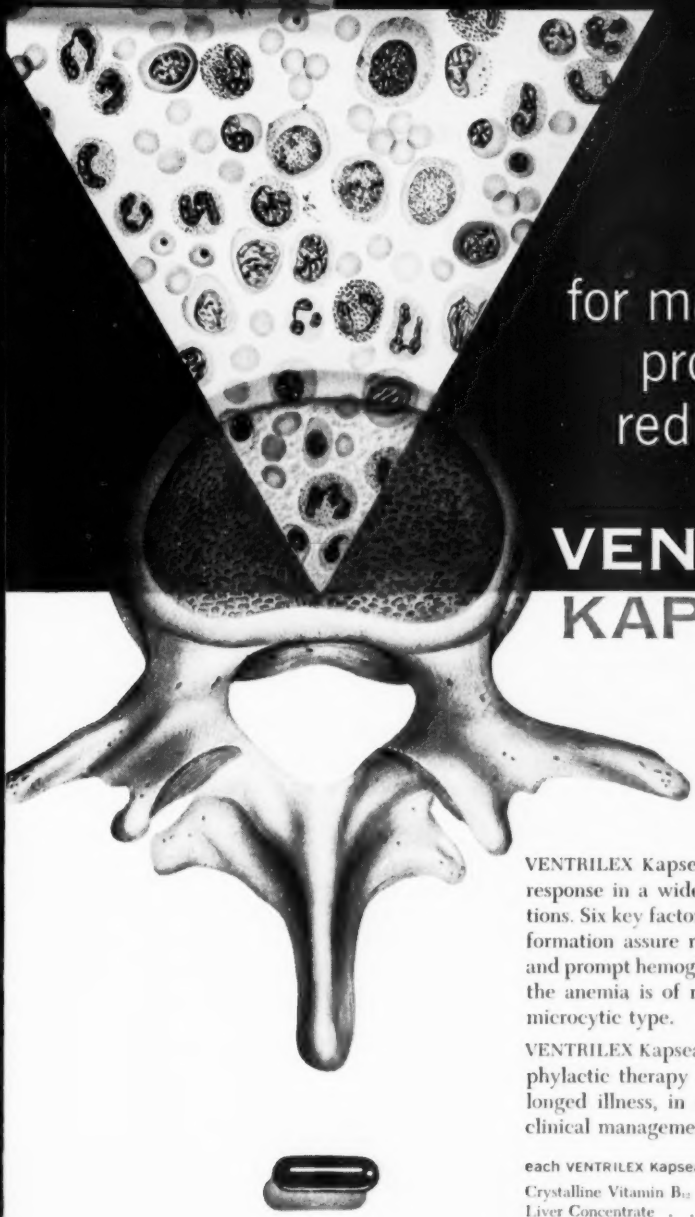

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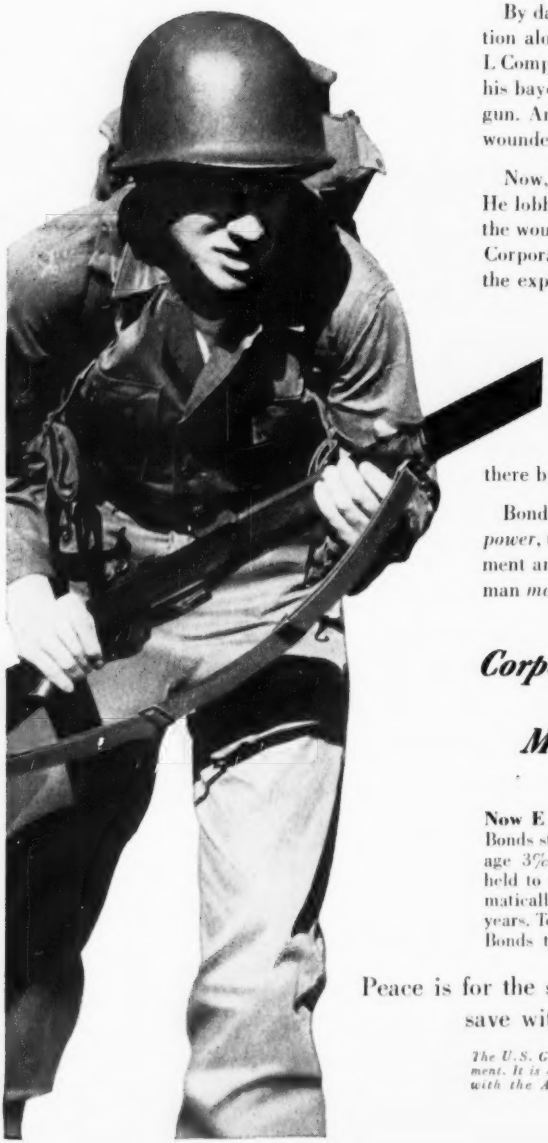

WITH FLARES AND WHISTLES and blaring bugles, the Reds had been attacking fanatically all night. Wave after wave they came, in overwhelming numbers.

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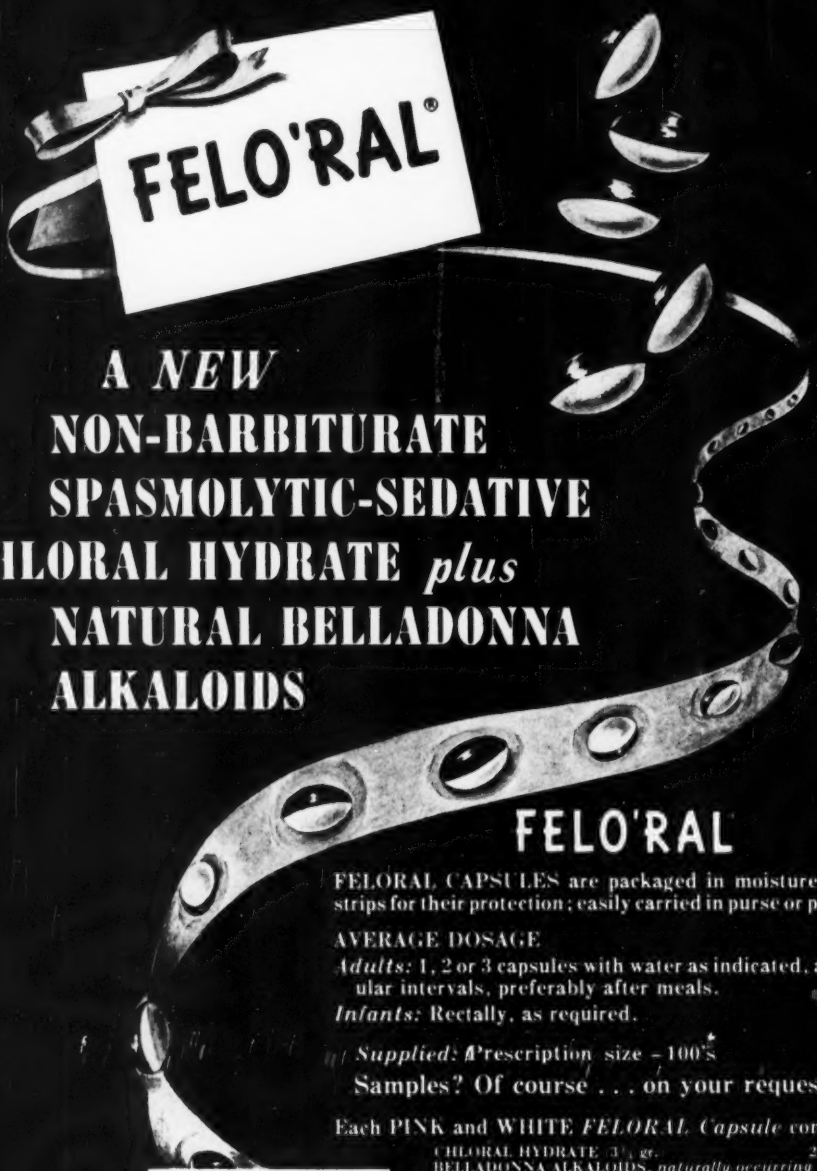
Donnalate incorporates the pharmacological features of both Robalate (for peptic ulcer) and Donnatal (for spasmolysis). Each Donnalate Tablet contains 0.5 Gm. dihydroxy aluminum aminoacetate, 8.1 mg. phenobarbital, 0.052 mg. hyoscyamine sulfate, 0.01 mg. atropine sulfate, and 0.003 mg. hyoscine hydrobromide (the equivalent of one Robalate tablet plus one-half of one Donnatal tablet).

A. H. ROBINS CO., INC. • *Ethical Pharmaceuticals of Merit since 1878* • RICHMOND 20, VIRGINIA

75th ANNIVERSARY



A *NEW* NON-BARBITURATE SPASMOLYTIC-SEDATIVE CHLORAL HYDRATE *plus* NATURAL BELLADONNA ALKALOIDS

FELO'RAL

FELORAL CAPSULES are packaged in moisture-proof strips for their protection; easily carried in purse or pocket.

AVERAGE DOSAGE

Adults: 1, 2 or 3 capsules with water as indicated, at regular intervals, preferably after meals.

Infants: Rectally, as required.

Supplied: Prescription size – 100's

Samples? Of course . . . on your request.

Each PINK and WHITE *FELORAL Capsule* contains:

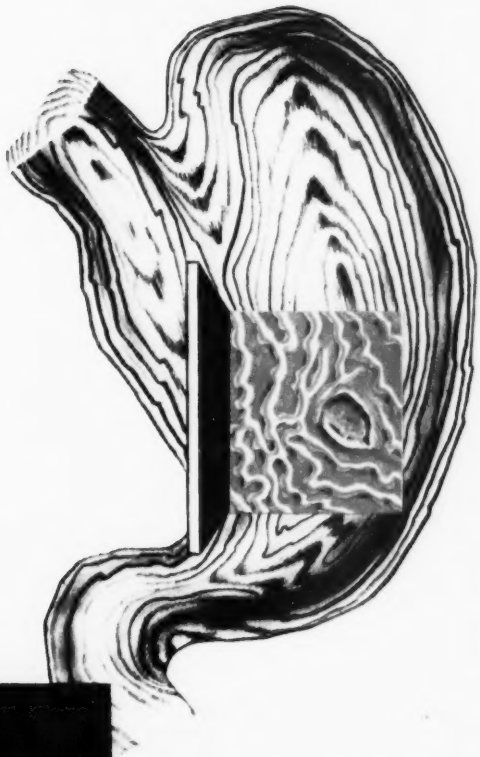
CHLORAL HYDRATE 3¾ gr.	250.0 mg.
BELLADONNA ALKALOIDS, *naturally occurring*	
HYOSUYAMINE	0.100 mg.
ATROPINE	0.020 mg.
HYOSCINE	0.006 mg.

Fellows MEDICAL MFG. CO. INC. Pharmaceuticals

pharmaceuticals since 1866

26 Christopher St., New York 14, N. Y.

Originators of CHLORAL HYDRATE in *Soft Gelatin Capsules*



maalox®

for gastric hyperacidity in peptic ulcer

Suspension MAALOX—Rorer provides the *hydroxides* of Magnesium and Aluminum in colloidal form . . . pleasantly flavored and highly acceptable, even with prolonged use. Relief of pain and epigastric distress is prompt and long-lasting. Freedom from constipation and side effects common to other antacids is noteworthy.

supplied:

in 355 cc. (12 fluidounce) bottles. Also in bottles of 100 tablets. (Each Maalox tablet is equivalent to 1 fluidram of Suspension.)

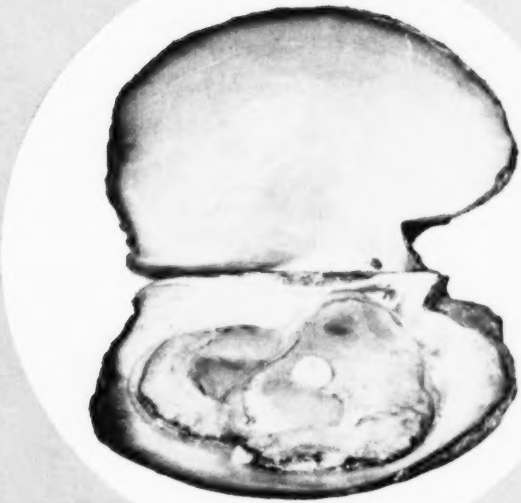
Samples will be sent promptly upon request.

ROHER

WILLIAM H. RORER, INC.

Drexel Bldg., Independence Square, Philadelphia 6, Penna.

ESTABLISHED IN 1910



What Nature Does for the Oyster . . .

AMPHOJEL® does for the peptic ulcer. Local physical protection by AMPHOJEL'S demulcent gel, plus the effect of its antacid component, hasten healing and relief of pain.

Wyeth

Philadelphia 2, Pa.